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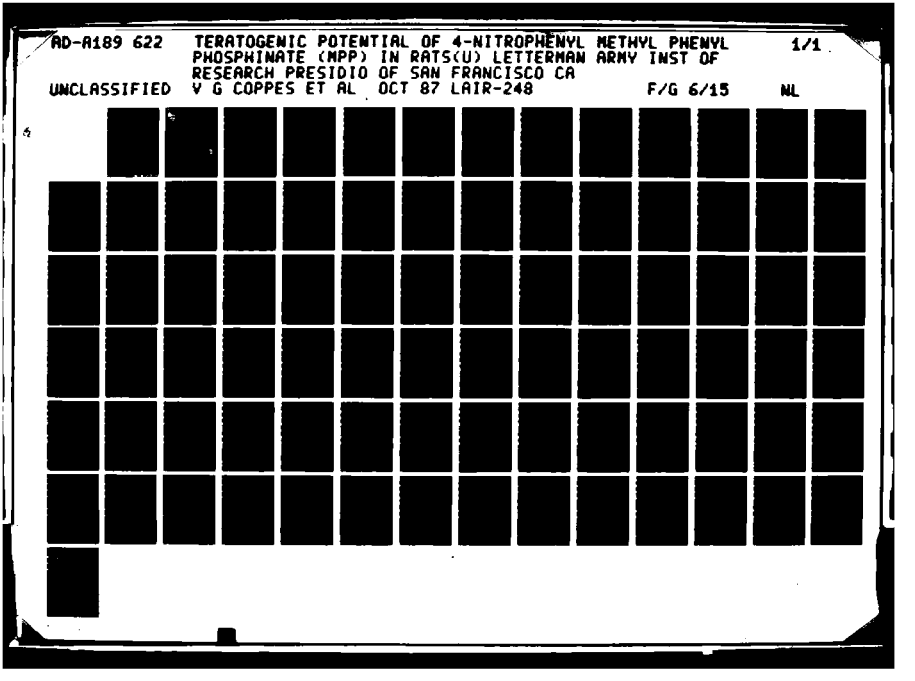

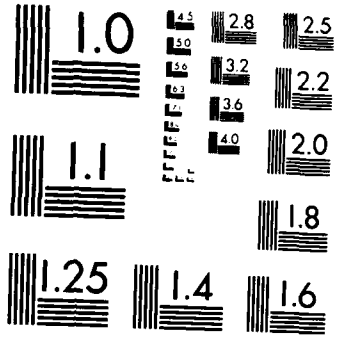


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*Institute Report No. 248*

# Teratogenic Potential of 4-Nitrophenyl Methyl Phenyl Phosphinate (MPP) in Rats

*Valerie G. Coppes, BS*
*Martha A. Hanes, DVM, CPT VC*
*and*
*Don W. Korte, Jr., PhD, MAJ MSC*



MAMMALIAN TOXICOLOGY BRANCH
DIVISION OF TOXICOLOGY

Toxicology Series: 63

OCTOBER 1987



LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129

**Teratogenic Potential of 4-Nitrophenyl Methyl Phenyl Phosphinate (MPP) in Rats (Toxicology Series 63)--Coppes, Hanes, and Korte**



**In conducting the research described in this report, the investigation adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care, Institute of Laboratory Animal Resources, National Research Council.**

**This material has been reviewed by Letterman Army Institute of Research and there is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.** ***(AR 360-5)***

Edwin S. Beatrice 22 Oct 87

**Edwin S. Beatrice** (date)
**COL, MC**
**Commanding**

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The teratogenic potential of 4-nitrophenyl methyl phenyl phosphinate (MPP) was tested in pregnant Sprague-Dawley rats. MPP was administered by oral gavage on Days 6 through 15 of gestation. Dose levels tested were 0, 0.12, 1.25, and 3.12 mg/kg/day. The vehicle contained 21.5% Tween 80, 18.5% absolute ethanol, 37.5% 50 mM citrate buffer, and 22.5% distilled water. Fetuses were delivered by cesarean section on Day 20 and weighed, examined externally, and either processed in Bouin's solution for visceral examination or alizarin red stain for skeletal examination. MPP did not produce dose-related teratogenic or embryotoxic effects in Sprague-Dawley rats.

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ABSTRACT

The teratogenic potential of 4-nitrophenyl methyl phenyl phosphinate (MPP) was tested in pregnant Sprague-Dawley rats. MPP was administered by oral gavage on Days 6 through 15 of gestation. Dose levels tested were 0, 0.12, 1.25, and 3.12 mg/kg/day. The vehicle contained 21.5% Tween 80, 18.5% absolute ethanol, 37.5% 50 mM citrate buffer, and 22.5% distilled water. Fetuses were delivered by cesarean section on Day 20 and weighed, examined externally, and either processed in Bouin's solution for visceral examination or alizarin red stain for skeletal examination. MPP did not produce dose-related teratogenic or embryotoxic effects in Sprague-Dawley rats.

KEY WORDS: Developmental Toxicology, Teratology, 4-Nitrophenyl Methyl Phenyl Phosphinate, Rat

## PREFACE

TYPE OF REPORT: Teratology GLP Study Report

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Letterman Army Institute of Research
Division of Toxicology
Presidio of San Francisco, CA 94129-6800

SPONSOR: US Army Medical Research and Development Command
Fort Detrick, MD 21701-5012

PROJECT: 35162772A875 Defense Against Chemical Agents
WU 304 Toxicity Testing of Phosphinate Compounds
APC TL04

GLP STUDY NUMBER: 82021

STUDY DIRECTOR: Don W. Korte, Jr., PhD, MAJ MSC

PRINCIPAL INVESTIGATOR: Martha A. Hanes, DVM, CPT, VC

CO-INVESTIGATOR: Valerie G. Coppes, BS

REPORT AND DATA MANAGEMENT: A copy of the final report, study protocol, addenda, raw data, SOPs, and an aliquot of the test compound will be retained in the LAIR Archives. Alizarin specimens will be retained in LAIR Pathology Archives.

TEST SUBSTANCE: 4-Nitrophenyl Methyl Phenyl Phosphinate (MPP)

INCLUSIVE STUDY DATES: 31 Aug 82- 15 March 83

OBJECTIVES: The purpose of this study was to determine the teratogenic and embryotoxic potential of MPP in pregnant Sprague-Dawley rats when administered orally during the period of organogenesis.

## ACKNOWLEDGMENTS

SP5 Justo Rodriguez, BS; SP5 Thomas P. Kellner, BA; SP5 Lawrence Mullen, BS; SP5 Paul D. Mauk, BS; SP4 Evelyn Zimmerman, Carolyn M. Lewis, MS, and Yvonne C. Johnson, BS, assisted in the research; COL John Marshall, PhD, and COL John Fruin, DVM, PhD, gave professional guidance; and Claire Lieske, US Army Medical Research Institute of Chemical Defense, provided the test compound, advice, and support.

SIGNATURES OF PRINCIPAL SCIENTISTS INVOLVED IN THE STUDY

We, the undersigned, declare that GLP Study 82021 was performed under our supervision, according to the procedures described herein, and that this report is an accurate record of the results obtained.

Don W. Korte 23 Oct 87

DON W. KORTE, JR., PHD / DATE
MAJ, MSC
Study Director

Valerie H Coppes 23 Oct 87

MARTHA A. HANES, DVM / DATE
CPT, VC
Principal Investigator

Valerie H Coppes 23 Oct 87

VALERIE G. COPPES, BS / DATE
DAC
Co-Principal Investigator

DEPARTMENT OF THE ARMY
LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129-6800

REPLY TO
ATTENTION OF:

SGRD-ULZ-QAA 7 Oct 87

MEMORANDUM FOR RECORD

SUBJECT: Report of GLP Compliance

1. I hereby certify that in relation to LAIR GLP Study 82021, the following inspections were made.

| | | |
|---|---|---|
| Insemination Determination | (Phase II) | 10 Feb 83 |
| Dosing and Weighing | (Phase I) | 19, 29 Oct 82 |
| | (Phase II) | 23, 24 Feb 83 |
| Unscheduled Sacrifice | (Phase I) | 26 Oct 83 |
| Scheduled Sacrifice | (Phase I) | 2 Nov 82 |
| | (Phase II) | 3 Mar 83 |
| Fetal Visceral Observations | (Phase II) | 21 Apr 83 |
| Fetal Skeletal Observations | (Phase II) | 5 Aug 84 |

2. The report entitled "Teratogenic Potential of 4-Nitrophenyl Methyl Phenyl Phosphinate (MPP) in Rats," Toxicology Series 63, and the raw data were audited on 11 Jun 87, 24 Sep 87, and 5 Oct 87.

Carolyn M. Lewis

CAROLYN M. LEWIS
C, Quality Assurance

TABLE OF CONTENTS

Table of Contents (continued)

Teratogenic Potential of 4-Nitrophenyl Methyl Phenyl Phosphinate in Rats -- Coppes et al

Organophosphinate compounds are being evaluated as prophylactic agents in organophosphate poisoning because of several disadvantages associated with conventional carbamate prophylaxis. The spontaneous rate of reactivation of carbamylated cholinesterase is relatively rapid with a t 1/2 for hydrolysis of 15 to 30 minutes (1). Consequently, there is no significant oxime effect on spontaneous reactivation of the carbamylated enzyme (2). Phosphinylated cholinesterases are reactivated more slowly with a t 1/2 for hydrolysis of 105.0 to 278.1 minutes (3). Therefore, oxime therapy significantly accelerates the rate of spontaneous reactivation of the phosphinylated enzyme (2). One of the phosphinates, 4-nitrophenyl methyl phenyl phosphinate (MPP), was selected for toxicologic evaluation based on the results of efficacy studies. LAIR was tasked to conduct the acute, subchronic, and teratogenic testing of MPP. This report presents results of a study to assess the teratogenic potential of MPP.

## Objective of the Study

The purpose of this study was to determine the teratogenic and embryotoxic potential of MPP in pregnant Sprague-Dawley rats when administered orally during the period of organogenesis.

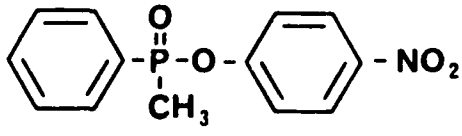
## MATERIALS

### Test Substance

Chemical Name: 4-Nitrophenyl Methyl Phenyl Phosphinate

Chemical Abstract Service Registry No.: None

Molecular Structure $C_{13}H_{12}NO_4P$




Molecular Weight: 277.2

Source: Ash Stevens Inc.
Detroit, Michigan 48202

Lot No.: XL 1X-40

Contaminants: None detected

Physical State/Color: Fluffy white crystals

Stability: Unstable at neutral and basic pH. Stable in acidified solution.

Other test substance information is presented in Appendix A.

## Rationale for Selection of the Vehicle

MPP is hydrolyzed in alkaline solutions. A vehicle was selected which would solubilize and stabilize the MPP. The vehicle selected was the same one used in the subchronic study (4). It contained 21.5% polysorbate 80 (Tween 80), 18.5% absolute ethanol, 37.5% 50 mM citrate buffer (pH 3.2), and 22.5% distilled water.

Additional information about the vehicle appears in Appendix A.

## Animal Data

Young adult Sprague-Dawley rats were obtained from Bantin-Kingman, Fremont, CA. The study was conducted in two phases due to the number of animals required. Eighty-five female and 41 male Sprague-Dawley rats were assigned to Phase I and 103 females and 52 males to Phase II. Two females from Phase I and 6 females from Phase II were selected at random for quality control necropsy. Animals were identified by sequentially numbered metal eartags. The weight ranges of rats were as follows:

| Phase | Receipt | | Start of Breeding | |
|---|---|---|---|---|
| | Females (gm) | Males (gm) | Females (gm) | Males (gm) |
| I | 250-296 | 249-286 | 261-331 | 406-504 |
| II | 193-308 | 223-299 | 240-327 | 391-589 |

A concurrently performed positive control study established the Sprague-Dawley rat as a sensitive test system for teratology studies at

LAIR (5). Historic data on sporadic malformations in rats have been well documented (6).

Husbandry

Upon arrival at LAIR, rats were housed individually in wire mesh rack cages with automatic water dispensers for the quarantine period. Animals were fed Purina Certified Rodent Chow 5002 (Ralston Purina Company, St Louis, MO) and tap water ad libitum throughout the study. No contaminants or naturally occurring substances were expected to influence the study. During breeding 1 male and 2 females were placed in polycarbonate cages with hardwood chip bedding, wire lids, and water bottles. After breeding the males were returned to the wire mesh rack cages; the females remained in the polycarbonate cages (2 females of the same dose group and breeding date per cage).

In Phase I, room temperature ranged between 64 and 74°F (17.8 and 23.3°C) and relative humidity between 58 and 77%. In Phase II, temperature ranged between 68 and 74°F (20.0 and 23.3°C) and relative humidity ranged between 47 and 70%. Several times during Phase II the relative humidity spiked to 90% for a short period of time. The fluctuation of relative humidity is not expected to have an impact on the outcome of the study. The photoperiod was 13 hours of light per day (0630-1930 hours).

METHODS

Methods used are described in detail in LAIR Teratology Testing Procedure OP-STX-40 (7) and were in accordance with Food and Drug Administration Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use (8).

Acclimation

Females were acclimatized before start of breeding for 8 and 18 days for Phases I and II, respectively. Males were acclimatized for at least 6 weeks.

Group Assignment

Females were assigned to groups according to LAIR OP-ISG-21 "Animal Randomization Procedure" (9) on the Data General ECLIPSE C/330 computer. Twenty random sequences of numbers corresponding to the number of dose groups were generated. When females became sperm positive, they were assigned to the dose group. Animals were selected for quality control necropsy according to a random number table.

## Dose Levels

Dose levels tested were 0, 3.12, 1.25, and 0.12 mg/kg/day. Sperm-positive females were dosed daily between 0800-1200 hours from Day 6 through Day 15 of gestation by oral intubation using an 18-gauge, 3-inch gastric gavage needle (Popper and Sons, Inc, New Hyde Park, NY 11040). Dosing was conducted without sedation or anesthetization of the animals. The test compound was administered orally as this is the expected human exposure route. The dose for each female was based on the Day 6 (Day 0 was the day sperm were detected in vagina) body weight, and that dose was used throughout the dosing period. Doses were calculated by a program on a Hewlett-Packard 98A calculator. The vehicle control was given at a constant volume of 1 ml per animal. Phase I females were dosed from 19 Oct 82 through 30 Oct 82. Phase II females were dosed from 14 Feb 83 through 27 Feb 83.

## Compound Preparation and Analysis

A quantity of vehicle sufficient for the entire dosing period of each phase was prepared. Stock solutions of 10 mg/ml test compound were prepared on 18, 22, and 28 Oct 82 for Phase I and on 13 and 18 Feb 83 for Phase II. These solutions were diluted with vehicle to obtain concentrations of 1.0 mg/ml for the high dose group, 0.4 mg/ml for the mid dose group, and 0.04 mg/ml for the low dose group. Aliquots of the dosing solutions and vehicle were pipetted into separate vials for each day of dosing and refrigerated to prevent contamination and decomposition. Before dosing the animals, the vials for that day were placed in a beaker of hot tap water for 15 to 30 minutes to bring the solutions to room temperature. The MPP solutions were assayed for hydrolyzed phosphinate by measuring its decomposition product, p-nitrophenol, with a Gilford Model 2400-S spectrophotometer (Appendix A).

## Breeding

After the quarantine period, each male was placed in the breeding cage with 2 females. Females were checked each morning for evidence of insemination. Day 0 for each female was the day sperm were observed in her vaginal smear. Sperm-positive females were assigned to dose groups as previously described. Sperm-positive females were separated from the males and placed with another female of similar breeding date and same dose group.

The breeding period was 3 days for Phase I and 5 days for Phase II. Matings were terminated when adequate numbers of females were sperm positive. Those females which were not sperm positive at the completion of the breeding period were removed from the study.

## Cesarean Section Procedure

Dams were weighed and euthanized with $CO_2$ gas on Day 20 of gestation. Non-pregnant females were examined and removed from the study. Gravid uteri were examined for number and placement of implantation sites, resorptions, and live and dead fetuses. Corpora lutea were not counted. The uterus and ovaries were removed, the dam examined for gross visceral signs of toxicity and reweighed. Fetuses were assigned alternately to either skeletal or visceral examination. Each fetus was sexed, weighed, and examined externally.

Fetuses assigned for skeletal examination were placed in 70% ethanol for several hours and eviscerated. They were then processed by the alizarin red S staining technique of Crary (10). After processing, the specimens were stored in glycerol with a few crystals of thymol to inhibit bacterial and mold growth. Fetuses assigned for visceral examination were placed in Bouin's solution. The body walls were pierced to allow penetration of the fixing solution.

## Observations and Records

Pregnant females were weighed on Day 0 and every other day through Day 20. Males were weighed weekly. Females were observed daily from Day 0 through Day 20 for clinical signs of toxicity, abortion, or premature delivery. Clinical signs were not recorded for Phase I animals except at cesarean section. Date, time, and amount of dosing solution administered were recorded during the daily dosing on Days 6 through 15. At sacrifice, uterine data, body weight, and results from gross examination of the dam were recorded. The gravid maternal weight was termed the "Gravid Day 20" weight. The maternal weight after removal of the uterus and fetuses was termed the "Corrected Day 20" weight.

Fetal weight, sex, and external examination findings from live fetuses were recorded. Bouin's fetuses were examined under low magnification by the modified Wilson freehand razor blade sectioning technique (11). The alizarin skeletons were examined under low magnification on a light box for degree of ossification, malformations, and alignment. The numbers of ossified sternebrae, ribs, caudal vertebrae, metacarpals, and metatarsals were counted.

## Schedule of Study Events

The study was divided into 2 phases to allow adequate time for animal care, fetal processing, and fetal examination. Upon arrival several animals from each phase were sent for quality control necropsy. The historical listing of study events is given in Appendix B.

## Statistical Analysis

The data were analyzed with BMDP software on a Data General ECLIPSE C/330 computer (12). Methods used are described by Hollander and Wolfe (13). Data from both phases were combined for analysis. The litter or litter mean was used as the experimental unit. All tests were run at the .05 level of significance. In this report the term "significant" indicates a statistically significant difference.

The maternal body weights, weight changes (Corrected Day 20 - Day 0), and fetal weights were compared by one-way analysis of variance. The variability of groups was compared using Levene's test for equal variances. If a significant result was obtained with Levene's test, the Welch's test was performed. The fetal examination findings were compared by the Chi-Square analysis. When differences were obtained with the Chi-Square analysis, the Fisher's Exact test was used to compare each MPP dose group with the vehicle control. The number of implantations, percent resorptions, percent live fetuses, and ossification data were compared by the Kruskal-Wallis test.

## Deviations from Original Protocol

Phase II deviated from the randomization as previously described, i.e. after sufficient animals had been assigned to 2 dose groups, these 2 numbers in the random sequence were skipped. Assignment of animals to the remaining 3 groups was continued in order to obtain a total of 20 pregnant females per dose group (total Phase I and Phase II). After combining Phase I and II the number of pregnant females per group ranged from 17 to 22.

The original protocol specified dosing from Day 6 through Day 17. However, in this study, animals were dosed from Day 6 through Day 15, the period of major organogenesis in the rat. The dose was calculated on the Day 6 body weight rather than Day 0 as stated in the protocol. Females were weighed every other day instead of every day. Pregnant females were housed 2 per cage rather than gang caged.

These deviations from the protocol did not affect the outcome of the study.

## Animals Excluded from Study

Due to inadvertent destruction of Bouin's processed fetuses, 2 females, 82D00759 and 82D00688, were eliminated from Phase I. Data from the skeletal-processed fetuses from these females were not included in this report. However, these data will be archived with other raw data from GLP Study #82021.

Nine animals were misdosed and subsequently they were removed from the study. Misdosing was confirmed by necropsy findings. These animals are listed in Appendix D.

Raw Data and Final Report Storage

A copy of the final report, study protocol, addenda, raw data, SOPs, and an aliquot of test compound will be retained in the LAIR Archives. Alizarin specimens will be retained in LAIR Pathology Archives.

## RESULTS

### Quality Control Necropsy

Tissues from Phase I quality control rats were normal by microscopic examination. Microscopic examination of Phase II tissues revealed sinusitis in all 6 females. Since all other tissues were normal and weight gain of the females was normal, the remaining females from that shipment were used for Phase II. The sinusitis appeared to have no effect on the results of the study.

### Maternal Data

The individual maternal weights are listed in Appendix C, and the group mean maternal weights are presented in Table 1. There were no significant differences in the weights or weight gains (Corrected Day 20 - Day 0) between the groups.

There were no maternal deaths in any of the dose groups. Individual maternal clinical signs are listed in Appendix D. Clinical signs for each dose group during the pretreatment (Day 0 through Day 5), treatment (Day 6 through Day 15) and posttreatment (Day 16 through Day 20) periods are found in Tables 2a,b, and c, respectively. The 3 MPP dose groups exhibited a dose-related increased incidence of clinical signs in comparison to the vehicle control group. Generally, these signs were seen in only a few animals per group, occurred randomly throughout the dosing period, and lasted 1 or 2 days. Clinical signs most frequently observed in the MPP dose groups included inactivity, yellow stained mouth, and ataxia.

The number of animals assigned to each group, number of animals that died during the study, and number and percent of animals that were pregnant are presented in Table 3. Pregnancy rate ranged from 68% in the vehicle control group to 96% in the MPP high dose group.

Cesarean/Fetal Data

The individual number of implantations, resorptions, percent resorptions, and number and percent of fetuses dead and live are listed in Appendix E. The number, sex, and mean fetal weight per litter are found in Appendix F. There were no differences in numbers of fetuses or fetal weights between groups. These data are summarized in Table 4.

Each fetus was examined for variations, retarded development, and anomalies both externally during the cesarean section delivery and again after visceral or skeletal processing. Descriptions of the examination findings were recorded. These descriptions with their corresponding incidences are listed in Appendices G, H, and I for the external, visceral, and skeletal examinations. Summaries for incidence of each anomaly and variant appear in Tables 5, 6, and 7. Fetuses with multiple anomalies and variants are listed in more than one descriptive category but are counted only once in the totals. Appendix J lists the number of fetuses per litter with anomalies and variants in the external, visceral, and skeletal examination findings. Appendix K shows the number of fetuses per litter with any anomalies and variants. Table 8 shows the group summary of the number of fetuses and the number of litters containing fetuses with anomalies and variants for the external, visceral, and skeletal examinations and a summary of number of fetuses and litters containing fetuses with any anomalies and variants. The MPP high and mid dose groups had significantly fewer fetuses with visceral variants, and the MPP high dose group had fewer fetuses with any variant than the vehicle control group. There were no significant differences in the number of fetuses with anomalies in the high, mid, and low MPP dose groups in comparison to the vehicle control group.

The litter mean numbers of sternebrae, caudal vertebrae, metacarpals, and metatarsals ossified are presented in Appendix L and the summaries by group are presented in Table 9. There were no group differences in the ossification data.

Table 1

Mean* Maternal Body Weights and Weight Changes†

| Day | Dosage of MPP (mg/kg/day) | | | |
|---|---|---|---|---|
| | 0 | 3.12 | 1.25 | 0.12 |
| 0 | 277.8 ± 22.1 | 276.6 ± 13.6 | 273.9 ± 14.1 | 284.0 ± 20.7 |
| 6 | 309.8 ± 21.6 | 308.4 ± 12.1 | 302.1 ± 14.8 | 314.2 ± 21.7 |
| 12 | 320.5 ± 23.5 | 320.1 ± 19.3 | 318.9 ± 19.0 | 327.1 ± 31.7 |
| 16 | 345.1 ± 25.0 | 351.5 ± 24.2 | 335.5 ± 23.3 | 355.1 ± 39.5 |
| Gravid 20 | 400.8 ± 36.8 | 406.0 ± 29.9 | 388.3 ± 44.3 | 405.2 ± 44.9 |
| Corrected 20 | 318.4 ± 33.8 | 314.2 ± 25.8 | 310.7 ± 23.8 | 315.5 ± 31.5 |
| Weight change† | 40.5 ± 19.6 | 37.6 ± 25.7 | 36.8 ± 20.5 | 31.6 ± 21.6 |

*Mean ± S.D. in g of pregnant animals.
†Group mean of [Corrected Day 20 weight - Day 0 weight].

Table 2a

Maternal Clinical Signs - Pretreatment (Days 0-5)

| | Dosage of MPP (mg/kg/day) | | | |
|---|---|---|---|---|
| Signs | 0 | 3.12 | 1.25 | 0.12 |
| Slight weight loss | 1 | 2 | | 2 |
| Blood, vaginal area | | 2 | 1 | 1 |

Table 2b

Maternal Clinical Signs - Treatment (Days 6-15)

| | Dosage of MPP (mg/kg/day) | | | |
|---|---|---|---|---|
| Signs | 0 | 3.12 | 1.25 | 0.12 |
| Signs of abortion | | | 1 | |
| Blood | | | | |
| mouth/nose | 1 | 1 | 1 | |
| vaginal area | | | 1 | |
| Cyanosis | | | 1 | |
| Foaming at mouth during misdosing | 1 | | | |
| Salivation | | 1 | | |
| Gasping | | 1 | | |
| Convulsion | | 1 | | |
| Hunched Posture | | | 1 | |
| Vomiting | | 1 | | |
| Ataxia | | | | 3 |
| Inactive | | 5 | 3 | 2 |
| Yellow stained mouth | | 3 | | |
| Yellow stained perianus | | 1 | | |
| Red stained nose/mouth | 1 | 1 | | 1 |
| Sound production | 2 | 3 | 2 | 1 |
| Mass (axillary) | | | 1 | |
| Weight loss | | | | 1 |

Table 2c

Maternal Clinical Signs
Posttreatment and at Sacrifice (Days 16-20)

| | Dosage of MPP (mg/kg/day) | | | |
|---|---|---|---|---|
| Signs | 0 | 3.12 | 1.25 | 0.12 |
| Weight loss | | | 1 | |
| Sound production | | | 1 | |
| Mass (axillary): | | | | |
| granulomatous tissue | | | 1 | |
| yellow fluid-filled | | | 1 | |
| Bladder stones | | | 1 | |
| Uterus: | | | | |
| enlarged, fluid filled | 1 | | | |
| Blood on nose | | 1 | | |
| Cyanosis | | | 1 | |
| Inactive | | | 1 | |

Table 3

Summary of Maternal Data

| | Dosage of MPP (mg/kg/day) | | | |
|---|---|---|---|---|
| | 0 | 3.12 | 1.25 | 0.12 |
| Number of animals assigned | 25 | 23 | 24 | 26 |
| Number of animals died | 0 | 0 | 0 | 0 |
| Percent of animals died | 0 | 0 | 0 | 0 |
| Number of animals pregnant | 17 | 22 | 20 | 21 |
| Percent of animals pregnant | 68 | 96 | 83 | 81 |

Table 4

Mean* Uterine and Litter Data

| | Dosage of MPP (mg/kg/day) | | | |
|---|---|---|---|---|
| | 0 | 3.12 | 1.25 | 0.12 |
| Number of litters | 17 | 22 | 20 | 21 |
| Mean values per litter | | | | |
| Number of implantations | 14.1 ± 4.9 | 15.8 ± 2.2 | 14.2 ± 4.2 | 14.7 ± 3.1 |
| Number of resorptions | 1.5 ± 1.5 | 1.4 ± 1.8 | 2.4 ± 3.6 | 1.3 ± 1.0 |
| Percent resorptions† | 10.8 ±12.0 | 9.4 ±11.6 | 16.9 ±22.4 | 8.4 ± 6.5 |
| Number of dead fetuses | 0 | 0 | 0 | 0.1 ± 0.2 |
| Percent dead fetuses§ | 0 | 0 | 0 | 0.3 ± 1.3 |
| Number of live fetuses | 12.6 ± 5.1 | 14.3 ± 2.8 | 11.9 ± 5.2 | 13.3 ± 2.8 |
| Percent live fetuses‡ | 89.2 ±12.0 | 90.5 ±11.6 | 83.1 ±22.4 | 91.3 ± 6.9 |
| Live fetuses: | | | | |
| Body weight (g) | 4.3 ± 1.0 | 4.1 ± 0.8 | 4.0 ± 0.7 | 4.2 ± 1.0 |
| Body weight, male fetuses (g) | 4.4 ± 1.0 | 4.1 ± 0.8 | 4.1 ± 0.9 | 4.4 ± 1.0 |
| Body weight, female fetuses (g) | 4.0 ± 0.8 | 4.0 ± 0.8 | 4.0 ± 0.6 | 4.2 ± 1.0 |
| Number of male fetuses | 6.9 ± 3.2 | 7.6 ± 2.2 | 6.6 ± 3.6 | 6.7 ± 2.6 |
| Percent male fetuses | 57.5 ±17.8 | 53.9 ±13.9 | 48.3 ±20.4 | 49.9 ±16.8 |

*Group mean ± S.D.
†Group mean of [resorptions per litter/implantations per litter] x 100
§Group mean of [dead fetuses per litter/implantations per litter] x 100
‡Group mean of [live fetuses per litter/implantations per litter] x 100

Table 5

Description and Incidence of Fetal External Examination Findings

| | Dosage of MPP (mg/kg/day) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | | 3.12 | | 1.25 | | 0.12 | |
| | No. | % | No. | % | No. | % | No. | % |
| No. of fetuses examined | 215 | | 315 | | 238 | | 280 | |
| Anomalies | | | | | | | | |
| Domed cranium | 1 | 0 | | | | | | |
| Cleft palate | | | | | 1 | 0 | | |
| Protruding tongue | 1 | 0 | | | | | | |
| Variants | | | | | | | | |
| Hemorrhage on cranium | | | 1 | 0 | | | | |

Table 6

Description and Incidence of Fetal Visceral Examination Findings

| | Dosage of MPP (mg/kg/day) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | | 3.12 | | 1.25 | | 0.12 | |
| | No. | % | No. | % | No. | % | No. | % |
| No. of fetuses examined | 105 | | 154 | | 113 | | 134 | |
| Anomalies | | | | | | | | |
| Cleft palate | | | | | 1 | 1 | | |
| Variants | | | | | | | | |
| Dilated brain ventricles | 1 | 1 | | | | | | |
| Cerebral hemorrhage | 3 | 3 | | | | | 2 | 1 |
| Microphthalmia | | | | | 1 | 1 | | |
| Small lens | 1 | 1 | | | | | | |
| Dilated renal pelvis | 11 | 11 | 9 | 6 | 8 | 7 | 18 | 13 |
| Small kidney | 6 | 6 | 1 | 1 | 2 | 2 | | |

Table 7

Description and Incidence of Fetal Skeletal Examination Findings

| | Dosage of MPP (mg/kg/day) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | | 3.12 | | 1.25 | | 0.12 | |
| | No. | % | No. | % | No. | % | No. | % |
| No. of fetuses examined | 110 | | 161 | | 125 | | 145 | |
| Anomalies | | | | | | | | |
| Domed cranium | 1 | 1 | | | | | | |
| Short maxilla with long mandible | 1 | 1 | | | | | | |
| Variants | | | | | | | | |
| Incomplete ossification: | | | | | | | | |
| Cranium | 14 | 13 | 15 | 9 | 6 | 5 | 8 | 6 |
| Vertebral centra | 7 | 6 | 8 | 5 | 10 | 8 | 11 | 8 |
| Pelvis | | | 1 | 1 | 2 | 2 | | |
| Sternebrae: | | | | | | | | |
| Fewer than 3 ossified | | | | | | | 1 | 1 |
| Large orbit | 1 | 1 | | | | | | |
| Wavy ribs | 2 | 2 | 3 | 2 | | | | |
| Short ribs | | | | | | | 1 | 1 |
| Lumbar rib | | | 6 | 4 | 8 | 6 | | |

Table 8

Summary of External, Visceral, and Skeletal Examination Findings

| | Dosage of MPP (mg/kg/day) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | | 3.12 | | 1.25 | | 0.12 | |
| | No. | % | No. | % | No. | % | No. | % |
| External Exam | | | | | | | | |
| Fetuses examined | 215 | | 315 | | 238 | | 280 | |
| Litters examined | 17 | | 22 | | 19 | | 21 | |
| Fetuses with anomalies | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Fetuses with variants | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Litters with anomalies | 1 | 6 | 0 | 0 | 1 | 5 | 0 | 0 |
| Litters with variants | 0 | 0 | 1 | 5 | 0 | 0 | 0 | 0 |
| Visceral Exam | | | | | | | | |
| Fetuses examined | 105 | | 154 | | 113 | | 134 | |
| Litters examined | 16 | | 22 | | 19 | | 21 | |
| Fetuses with anomalies | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| Fetuses with variants | 22 | 21 | 10* | 6 | 11* | 10 | 19 | 14 |
| Litters with anomalies | 0 | 0 | 0 | 0 | 1 | 5 | 0 | 0 |
| Litters with variants | 8 | 50 | 7 | 32 | 6 | 32 | 11 | 52 |
| Skeletal Exam | | | | | | | | |
| Fetuses examined | 110 | | 161 | | 125 | | 145 | |
| Litters examined | 17 | | 22 | | 19 | | 21 | |
| Fetuses with anomalies | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Fetuses with variants | 21 | 19 | 28 | 18 | 24 | 19 | 20 | 14 |
| Litters with anomalies | 1 | 6 | 0 | 0 | 0 | 0 | 0 | 0 |
| Litters with variants | 9 | 53 | 15 | 68 | 11 | 58 | 9 | 43 |
| Summary of External, Visceral, Skeletal | | | | | | | | |
| Fetuses examined | 215 | | 315 | | 238 | | 280 | |
| Litters examined | 17 | | 22 | | 19 | | 21 | |
| Fetuses with anomalies | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 |
| Fetuses with variants | 43 | 20 | 39* | 13 | 35 | 15 | 39 | 14 |
| Litters with anomalies | 1 | 6 | 0 | 0 | 1 | 5 | 0 | 0 |
| Litters with variants | 11 | 65 | 17 | 77 | 13 | 68 | 15 | 71 |

*Significantly different from the control group.

Table 9

Summary of Ossification Data*

| | Dosage of MPP (mg/kg/day) | | | |
|---|---|---|---|---|
| | 0 | 3.12 | 1.25 | 0.12 |
| Sternebrae | 5.40 ± 0.49 | 5.45 ± 0.52 | 5.45 ± 0.52 | 5.19 ± 0.79 |
| Caudal vertebrae | 3.66 ± 1.12 | 3.52 ± 1.06 | 3.51 ± 0.89 | 3.70 ± 1.35 |
| Metacarpals | 6.60 ± 0.84 | 6.46 ± 0.70 | 6.44 ± 0.76 | 6.57 ± 0.90 |
| Metatarsals | 8.08 ± 0.52 | 8.09 ± 0.61 | 8.11 ± 0.65 | 8.17 ± 0.61 |

*Mean values calculated on a per litter basis.

DISCUSSION

This study was undertaken to evaluate the teratogenic and embryotoxic effects of 4-nitrophenyl methyl phenyl phosphinate (MPP). Dose levels were selected based upon results of acute and subchronic toxicity studies (14, 4). The high dose of MPP produced collapse, changes in respiratory rate and depth, tremors, gasping, excessive salivation, piloerection or rough coat, loss of equilibrium, humpback, red and yellow stains on anterior and posterior body sections, cyanosis, and vomiting in the 14-day subchronic toxicity study. Clinical signs of toxicity observed in this study were similar at comparable dose levels to those reported in the 14-day subchronic study. The dose levels selected for this study produced a dose-related increase in the incidence of clinical signs observed in the treated animals versus the controls.

Evidence for a teratogenic effect is considered to be a dose-related increase in frequency of major malformations in the test groups compared to the vehicle control group. For this study, major malformations, such as cleft palate, protruding tongue, abnormal cranium and mandible, were considered anomalies. Minor variations in the number or degree of ossification of sternebrae, caudal vertebrae, metatarsals, metacarpals, skull bones, vertebral centra, dilated renal pelvis, dilated ventricles of the brain, cerebral hemorrhage, and ribs (wavy, short, and lumbar) were considered to be variants as they do not represent a specific malformation but a transient phase in development. However, if variants occurred at significantly higher frequencies in the test groups compared to the vehicle control group, this would be considered evidence of embryotoxicity. Decreased body size and edema also are manifestations of embryotoxicity. Fetal deaths or resorptions are considered manifestations of maternal toxicity, not evidence of teratogenicity (15).

MPP did not produce dose-related teratogenic or embryotoxic effects. The MPP dose groups contained 1 fetus with a major anomaly, cleft palate in the mid dose group. This represented a 0.42% anomaly rate for that group (total 238 fetuses) which is similar to that found in the vehicle control group. Visceral variant findings for the low dose group were similar to those found in the vehicle control group, with the mid and high dose groups having significantly fewer fetuses with variants. Skeletal variant findings were similar to the vehicle control with the exception that 6% in the mid and 4% in the high MPP dose groups had supernumerary lumbar ribs. The presence of supernumerary lumbar ribs is one of the most common variants in rats (6).

One vehicle control fetus had anomalies of the head characterized by domed-shaped cranium, protruding tongue, and short maxilla with long mandible. This represents a 0.47% anomaly rate for fetuses in that

group (total 215 fetuses). Palmer (6) reported an incidence of spontaneous malformations in the rat of 0.41% major malformations from 51,349 control fetuses.

The vehicle control and MPP dose groups had a higher incidence of nondose-related visceral and skeletal variants than published control data (6). The incidence of visceral variants was 21% in the vehicle control group and 6%, 10%, and 14% in the MPP high, mid, and low dose groups, respectively. Dilated renal pelvis occurred in 11% of the vehicle control fetuses and in 13% of the MPP low dose fetuses versus a published control incidence of 6 to 7%. However, this published control rate included renal dilation as a variant only when no pelvic projections were present (6), whereas in our study renal pelvic dilation was recorded as a variant even though some pelvic projections were present. Other visceral variants were small kidney, cerebral hemorrhage, dilated ventricles of brain, and microphthalmia. Likewise, 2 skeletal variants, incomplete ossification of cranium and vertebral centra, occurred at a higher frequency in all groups than in published control data (6).

Two factors may have contributed to the incidence of variants in the vehicle control and MPP dose groups. The vehicle contained 18.5% absolute ethanol. Fetal alcohol syndrome (FAS) is characterized by growth retardation and an increased frequency of major and minor malformations. Mice treated with alcohol (3.75 ml/kg) on Day 7 produced a high frequency of fetuses with defects of the head, microphthalmia, cleft palate, and a characteristic profile in which the maxilla failed to overlap the mandible (16). Even though rats in this study received a lower daily dose (0.58 ml/kg ETOH), they did receive it on Days 6 through 15. Thus, two fetuses in the vehicle control group, one fetus with a domed cranium, short maxilla, and long mandible and one fetus with small lens, and one fetus in the mid dose (MPP) group with cleft palate and microphthalmia may represent a fetal effect of the ethanol in the vehicle.

The vehicle also contained 21.5% Tween 80. The Tween component of the vehicle may not be inert in teratological experiments. Kocher-Becker et al (17) reported that Tween 20 when given to mice was not merely a solubilizing agent but a teratogen in itself. When given to Swiss mice as a single injection of 1.0 ml/kg on Day 9 of gestation, Tween 20 produced malformations and variants, mostly involving the vertebrae and ribs, in 11.8% of the fetuses in comparison to 0.8% in the control. At higher dose levels, Tween 20 produced malformations with striking similarities to those produced by thalidomide. Although the rats in this study received 0.67 ml Tween 80/kg on Days 6 through 15, variations in ribs and vertebral centra ossification possibly could be attributed to the Tween in the vehicle. In comparing Tween 20, Tween 40, Tween 60, and Tween 80, Bresch and Ockenfels (18) found that the 4 different Tween surfactants acted similarly and all 4 strongly

influenced development of the sea urchin embryo.

## CONCLUSION

When given in daily oral doses of 0.12, 1.25, and 3.12 mg/kg/day from Days 6 through 15 of pregnancy, MPP did not produce dose-related teratogenic or embryotoxic effects in Sprague-Dawley rats.

## RECOMMENDATION

If efficacy data warrant continued development, the teratogenic potential of MPP should be evaluated in a second species, preferably the rabbit, to confirm its low risk. If additional teratology studies are conducted, a new vehicle should be developed which would not only insure the stability of the test compound but also would be more compatible with teratologic evaluations.

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APPENDICES

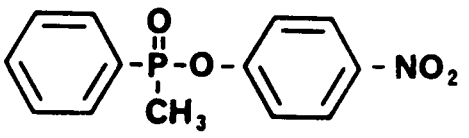
CHEMICAL DATA

Test Substance

Chemical Name: 4-Nitrophenyl Methyl Phenyl Phosphinate

Chemical Abstract Service Registry No.: None

Molecular Structure $C_{13}H_{12}NO_4P$




Source: Ash Stevens Inc.
Detroit, Michigan 48202

Lot No.: XL 1X-40

Contaminants: None detected

Molecular Weight: 277.2

Melting Point: 85-86°C

Physical State/Color: Fluffy white crystals

Stability: Unstable at neutral and basic pH. Stable in acidified solution. In preliminary studies MPP was relatively stable in vehicle for 8 days as determined by spectrophotometric measurement of p-nitrophenol (Spectrophotometric measure of p-nitrophenol for phosphinate determination. LAIR Standard Operating Procedure OP-STX-49. Letterman Army Institute of Research, Presidio of San Francisco, CA. 28 Dec 1981.)

Vehicle Substances

Chemical Name: Polysorbate 80 (Tween 80)

Chemical Abstract Service Registry No.: 9005-65-6

Source: Fisher Scientific Co.
Fairlawn, New Jersey 07410

Lot No.: 713137

Chemical Name: Ethanol, anhydrous

Chemical Abstract Service Registry No.: 64-17-5

Phase I

Source: U.S. Industrial Chemicals
Tuscola, Illinois 61953

Lot No.: 136

Phase II

Source: Aaper Alcohol and Chemical Co.
Louisville, Kentucky 40214

Lot No.: DSP-KY-73

Chemical Name: Citric acid, monohydrate

Chemical Abstract Service Registry No.: 77-92-9

Chemical Name: Sodium citrate

Chemical Abstract Service Registry No.: None

Analysis of Dosing Solution

| Date of Preparation | Date of Analysis | Dosing Solution mg/ml | Intact Phosphinate* mg/ml |
|---|---|---|---|
| Phase I | | | |
| 18 Oct 82 | 18 Oct 82 | 0.04 | 0.042 |
| 18 Oct 82 | 18 Oct 82 | 0.40 | 0.402 |
| 18 Oct 82 | 18 Oct 82 | 1.00 | 1.042 |
| 18 Oct 82 | 19 Oct 82 | 0.04 | 0.036 |
| 18 Oct 82 | 19 Oct 82 | 0.40 | 0.371 |
| 18 Oct 82 | 19 Oct 82 | 1.00 | 0.950 |
| 18 Oct 82 | 22 Oct 82 | 0.04 | 0.038 |
| 18 Oct 82 | 22 Oct 82 | 0.40 | 0.375 |
| 18 Oct 82 | 22 Oct 82 | 1.00 | 0.950 |
| 22 Oct 82 | 22 Oct 82 | 0.04 | 0.042 |
| 22 Oct 82 | 22 Oct 82 | 0.40 | 0.398 |
| 22 Oct 82 | 22 Oct 82 | 1.00 | 1.131 |
| 28 Oct 82 | 28 Oct 82 | 0.04 | 0.037 |
| 28 Oct 82 | 28 Oct 82 | 0.40 | 0.395 |
| 28 Oct 82 | 28 Oct 82 | 1.00 | 1.119 |
| Phase II | | | |
| 13 Feb 83 | 13 Feb 83 | 1.00 | 0.898 |
| 18 Feb 83 | 19 Feb 83 | 1.00 | 0.935 |

* Determined by spectrophotometric measurement of p-nitrophenol for phosphinate determination.

Historical Listing of Major Study Events

| | |
|---|---|
| 29 Jun 82 | Date of protocol request. |
| 31 Aug 82 | 41 male rats arrived at LAIR for Phase I. |
| 5 Oct 82 | 85 females arrived at LAIR for Phase I. |
| 12 - 15 Oct 82 | Phase I breeding. |
| 19 - 30 Oct 82 | Sperm-positive females dosed. |
| 2 - 4 Nov 82 | Cesarean sections on sperm-positive females. |
| 13 Dec 82 | 52 males arrived at LAIR for Phase II. |
| 20 Jan 83 | 103 females arrived at LAIR for Phase II. |
| 7 - 12 Feb 83 | Phase II breeding. |
| 14 - 27 Feb 83 | Sperm-positive females dosed. |
| 28 Feb - 4 Mar 83 | Cesarean sections on sperm-positive females. |

Individual Maternal Body Weights (Grams) - Vehicle Animals

| Maternal ID | Day 0 Age | Date of Breeding | Date of Sacrifice | Pregnant | Day of Gestation 0 | 6 | 12 | 16 | Gravid 20 | Correct 20 | Weight Change |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 82D00682 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 270 | 295 | 317 | 350 | 402 | 317 | 47 |
| 82D00691 | 131 | 14 Oct 82 | 03 Nov 82 | Yes | 299 | 338 | 343 | 381 | 459 | 356 | 57 |
| 82D00694 | (132) | 15 Oct 82 | 04 Nov 82 | No | (311) | (318) | (318) | (307) | (313) | (313) | (2) |
| 82D00698 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 270 | 307 | 307 | 341 | 407 | 327 | 57 |
| 82D00703 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 267 | 306 | 335 | 328 | 343 | 327 | 60 |
| 82D00719 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 303 | 333 | 359 | 389 | 449 | 346 | 43 |
| 82D00724 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 286 | 319 | 302 | 333 | 365 | 311 | 25 |
| 82D00743 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 262 | 306 | 302 | 343 | 408 | 327 | 65 |
| 82D00749 | (131) | 14 Oct 82 | 03 Nov 82 | No | (291) | (320) | (328) | (329) | (316) | (316) | (25) |
| 82D00751 | 132 | 15 Oct 82 | 04 Nov 82 | Yes | 331 | 349 | 359 | 387 | 443 | 382 | 51 |
| 83D00001 | 98 | 09 Feb 83 | 01 Mar 83 | Yes | 263 | 287 | 303 | 313 | 340 | 279 | 16 |
| 83D00013 | (97) | 08 Feb 83 | 28 Feb 83 | No | (277) | (278) | (289) | (296) | (302) | (302) | (25) |
| 83D00019 | 98 | 09 Feb 83 | 01 Mar 83 | Yes | 272 | 316 | 322 | 357 | 395 | 278 | 6 |
| 83D00026 | (97) | 08 Feb 83 | 28 Feb 83 | No | (314) | (331) | (325) | (314) | * | * | * |
| 83D00039 | 97 | 08 Feb 83 | 28 Feb 83 | Yes | 296 | 329 | 337 | 350 | 402 | 353 | 57 |
| 83D00041 | (98) | 09 Feb 83 | 1 Mar 83 | No | (282) | (324) | (317) | (313) | (300) | (300) | (18) |
| 83D00049 | (100) | 11 Feb 83 | 03 Mar 83 | No | (281) | (309) | (298) | (297) | (290) | (290) | (9) |
| 83D00052 | (97) | 08 Feb 83 | 28 Feb 83 | No | (285) | (314) | (317) | (328) | (332) | (332) | (47) |
| 83D00062 | 99 | 10 Feb 83 | 02 Mar 83 | Yes | 265 | 282 | 302 | 334 | 373 | 273 | 8 |
| 83D00063 | 98 | 09 Feb 83 | 01 Mar 83 | Yes | 240 | 273 | 296 | 312 | 370 | 282 | 42 |
| 83D00070 | 100 | 11 Feb 83 | 03 Mar 83 | Yes | 265 | 294 | 311 | 343 | 385 | 285 | 20 |
| 83D00076 | 98 | 09 Feb 83 | 01 Mar 83 | Yes | 257 | 294 | 279 | 315 | 388 | 282 | 25 |
| 83D00082 | 101 | 12 Feb 83 | 04 Mar 83 | Yes | 301 | 335 | 351 | * | 451 | 356 | 55 |
| 83D00087 | (100) | 11 Feb 83 | 03 Mar 83 | No | (262) | (295) | (297) | (293) | (286) | (286) | (24) |
| 83D00096 | 101 | 12 Feb 83 | 04 Mar 83 | Yes | 276 | 303 | 324 | * | 434 | 331 | 55 |

* Weight not obtained.

Individual Maternal Body Weights (Grams) - 3.12 mg/kg/day MPP Animals

| Maternal ID | Day 0 Age | Date of Breeding | Date of Sacrifice | Pregnant | Day of Gestation 0 | 6 | 12 | 16 | Gravid 20 | Correct 20 | Weight Change |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 82D00681 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 284 | 313 | 330 | 369 | 438 | 314 | 30 |
| 82D00696 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 298 | 329 | 325 | 366 | 431 | 352 | 54 |
| 82D00699 | 131 | 14 Oct 82 | 03 Nov 82 | Yes | 269 | 308 | 320 | 348 | 406 | 356 | 87 |
| 82D00704 | 131 | 14 Oct 82 | 03 Nov 82 | Yes | 274 | 305 | 312 | 347 | 424 | 321 | 47 |
| 82D00706 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 264 | 307 | 338 | 373 | 426 | 343 | 79 |
| 82D00723 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 279 | 300 | 317 | 339 | 401 | 306 | 27 |
| 82D00728 | 131 | 14 Oct 82 | 03 Nov 82 | Yes | 293 | 314 | 315 | 352 | 392 | 316 | 23 |
| 82D00734 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 274 | 308 | 334 | 373 | 416 | 318 | 44 |
| 82D00739 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 286 | 324 | 348 | 390 | 448 | 337 | 51 |
| 82D00750 | 131 | 14 Oct 82 | 03 Nov 82 | Yes | 290 | 321 | 335 | 378 | 445 | 342 | 52 |
| 82D00752 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 277 | 309 | 350 | 394 | 447 | 340 | 63 |
| 83D00010 | 98 | 09 Feb 83 | 01 Mar 83 | Yes | 258 | 291 | 314 | 335 | 362 | 271 | 13 |
| 83D00016 | 97 | 08 Feb 83 | 28 Feb 83 | Yes | 252 | 286 | 292 | 310 | 388 | 292 | 40 |
| 83D00020 | 97 | 08 Feb 83 | 28 Feb 83 | Yes | 254 | 289 | 319 | 355 | 430 | 328 | 74 |
| 83D00024 | 98 | 09 Feb 83 | 01 Mar 83 | Yes | 266 | 312 | 331 | 349 | 386 | 287 | 2[illegible] |
| 83D00040 | (99) | 10 Feb 83 | 02 Mar 83 | No | (264) | (278) | (273) | (272) | (255) | (255) | (-9) |
| 83D00042 | 97 | 08 Feb 83 | 28 Feb 83 | Yes | 269 | 294 | 288 | 326 | 388 | 289 | 20 |
| 83D00044 | 98 | 09 Feb 83 | 01 Mar 83 | Yes | 289 | 323 | 287 | 331 | 369 | 284 | -5 |
| 83D00047 | 99 | 10 Feb 83 | 02 Mar 83 | Yes | 278 | 303 | 287 | 297 | 346 | 265 | -13 |
| 83D00050 | 98 | 09 Feb 83 | 01 Mar 83 | Yes | 301 | 323 | 348 | 366 | 389 | 314 | 13 |
| 83D00059 | 97 | 08 Feb 83 | 28 Feb 83 | Yes | 273 | 307 | 306 | 353 | 437 | 323 | 50 |
| 83D00073 | 99 | 10 Feb 83 | 02 Mar 83 | Yes | 269 | 298 | 324 | 351 | 390 | 293 | 24 |
| 83D00101 | 100 | 11 Feb 83 | 03 Mar 83 | Yes | 289 | 320 | 323 | 331 | 373 | 322 | 33 |

Individual Maternal Body Weights (Grams) - 1.25 mg/kg/day MPP Animals

| Maternal ID | Day 0 Age | Date of Breeding | Date of Sacrifice | Pregnant | Day of Gestation 0 | 6 | 12 | 16 | Gravid 20 | Correct 20 | Weight Change |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 82D00684 | (130) | 13 Oct 82 | 02 Nov 82 | No | (308) | (324) | (338) | (321) | (325) | (325) | (17) |
| 82D00689 | 132 | 15 Oct 82 | 04 Nov 82 | Yes | 291 | 312 | 318 | 344 | 396 | 338 | 47 |
| 82D00697 | 132 | 15 Oct 82 | 04 Nov 82 | Yes | 271 | 300 | 290 | 338 | 416 | 313 | 42 |
| 82D00700 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 287 | 314 | 345 | 376 | 454 | 335 | 48 |
| 82D00705 | (132) | 15 Oct 82 | 04 Nov 82 | No | (281) | (304) | (298) | (284) | (284) | (284) | (3) |
| 82D00708 | (131) | 14 Oct 82 | 03 Nov 82 | No | (293) | (326) | (307) | (315) | (298) | (298) | (5) |
| 82D00710 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 276 | 302 | 332 | 354 | 418 | 330 | 54 |
| 82D00715 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 282 | 316 | 337 | 366 | 447 | 347 | 65 |
| 82D00731 | 131 | 14 Oct 82 | 03 Nov 82 | Yes | 261 | 307 | 304 | 320 | 402 | 306 | 45 |
| 82D00735 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 278 | 293 | 319 | 324 | 355 | 325 | 47 |
| 82D00740 | 132 | 15 Oct 82 | 04 Nov 82 | Yes | 303 | 331 | 320 | 336 | 366 | 317 | 14 |
| 82D00745 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 268 | 292 | 313 | 353 | 416 | 302 | 34 |
| 82D00763 | 131 | 14 Oct 82 | 03 Nov 82 | Yes | 280 | 303 | 312 | 338 | 392 | 317 | 37 |
| 83D00003 | 101 | 12 Feb 83 | 04 Mar 83 | Yes | 266 | 292 | 292 | * | 365 | 279 | 13 |
| 83D00014 | 97 | 08 Feb 83 | 28 Feb 83 | Yes | 262 | 301 | 301 | 311 | 344 | 305 | 43 |
| 83D00029 | 98 | 09 Feb 83 | 01 Mar 83 | Yes | 294 | 322 | 357 | 292 | 285 | 285 | -9 |
| 83D00031 | 99 | 10 Feb 83 | 02 Mar 83 | Yes | 249 | 282 | 296 | 305 | 330 | 294 | 45 |
| 83D00032 | 99 | 10 Feb 83 | 02 Mar 83 | Yes | 288 | 323 | 352 | 373 | 458 | 356 | 68 |
| 83D00037 | 98 | 09 Feb 83 | 01 Mar 83 | Yes | 257 | 280 | 316 | 345 | 429 | 312 | 55 |
| 83D00051 | (97) | 08 Feb 83 | 28 Feb 83 | No | (279) | (311) | (297) | (292) | (292) | (292) | (13) |
| 83D00056 | 97 | 08 Feb 83 | 28 Feb 83 | Yes | 266 | 309 | 312 | 333 | 388 | 312 | 46 |
| 83D00060 | 98 | 09 Feb 83 | 01 Mar 83 | Yes | 256 | 278 | 309 | 319 | 357 | 268 | 12 |
| 83D00067 | 97 | 08 Feb 83 | 28 Feb 83 | Yes | 268 | 289 | 317 | 306 | 354 | 274 | 6 |
| 83D00077 | 98 | 09 Feb 83 | 01 Mar 83 | Yes | 275 | 295 | 336 | 341 | 393 | 298 | 23 |

* Weight not obtained.

Individual Maternal Body Weights (Grams) - 0.12 mg/kg/day MPP Animals

| Maternal ID | Day 0 Age | Date of Breeding | Date of Sacrifice | Pregnant | Day of Gestation 0 | 6 | 12 | 16 | Gravid 20 | Correct 20 | Weight Change |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 82D00686 | (130) | 13 Oct 82 | 02 Nov 82 | No | (283) | (306) | (298) | (275) | (292) | (292) | (9) |
| 82D00690 | (131) | 14 Oct 82 | 03 Nov 82 | No | (286) | (295) | (316) | (305) | (304) | (304) | (18) |
| 82D00693 | 131 | 14 Oct 82 | 03 Nov 82 | Yes | 288 | 320 | 334 | 368 | 431 | 336 | 48 |
| 82D00702 | (131) | 14 Oct 82 | 03 Nov 82 | No | (282) | (312) | (300) | (304) | (285) | (285) | (3) |
| 82D00714 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 310 | 338 | 365 | 407 | 482 | 352 | 42 |
| 82D00717 | (130) | 13 Oct 82 | 02 Nov 82 | No | (276) | (306) | (315) | (293) | (285) | (285) | (9) |
| 82D00727 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 308 | 346 | 370 | 416 | 510 | 395 | 87 |
| 82D00729 | 132 | 15 Oct 82 | 04 Nov 82 | Yes | 282 | 299 | 310 | 342 | 390 | 313 | 31 |
| 82D00741 | (130) | 13 Oct 82 | 02 Nov 82 | No | (282) | (306) | (312) | (288) | (289) | (289) | (7) |
| 82D00746 | 130 | 13 Oct 82 | 02 Nov 82 | Yes | 281 | 310 | 329 | 348 | 401 | 319 | 38 |
| 82D00764 | 131 | 14 Oct 82 | 03 Nov 82 | Yes | 261 | 298 | 267 | 285 | 326 | 286 | 25 |
| 83D00004 | 97 | 08 Feb 83 | 28 Feb 83 | Yes | 288 | 317 | 333 | 362 | 414 | 322 | 34 |
| 83D00011 | 100 | 11 Feb 83 | 03 Mar 83 | Yes | 265 | 285 | 292 | 318 | 378 | 299 | 34 |
| 83D00015 | 98 | 09 Feb 83 | 01 Mar 83 | Yes | 282 | 308 | 337 | 350 | 424 | 325 | 43 |
| 83D00023 | 97 | 08 Feb 83 | 28 Feb 83 | Yes | 266 | 301 | 322 | 339 | 394 | 316 | 50 |
| 83D00025 | 098 | 09 Feb 83 | 01 Mar 83 | Yes | 253 | 289 | 260 | 276 | 341 | 249 | -4 |
| 83D00030 | 99 | 10 Feb 83 | 02 Mar 83 | Yes | 298 | 332 | 342 | 380 | 376 | 287 | -11 |
| 83D00034 | 98 | 09 Feb 83 | 01 Mar 83 | Yes | 327 | 357 | 381 | 402 | 444 | 339 | 12 |
| 83D00038 | 99 | 10 Feb 83 | 02 Mar 83 | Yes | 288 | 328 | 358 | 390 | 448 | 338 | 50 |
| 83D00043 | 100 | 11 Feb 83 | 03 Mar 83 | Yes | 295 | 324 | 324 | 332 | 391 | 322 | 27 |
| 83D00054 | 97 | 08 Feb 83 | 28 Feb 83 | Yes | 293 | 317 | 324 | 357 | 407 | 315 | 22 |
| 83D00069 | 98 | 09 Feb 83 | 01 Mar 83 | Yes | 295 | 320 | 344 | 374 | 410 | 307 | 12 |
| 83D00075 | 99 | 10 Feb 83 | 02 Mar 83 | Yes | 254 | 287 | 313 | 309 | 355 | 290 | 36 |
| 83D00078 | 98 | 09 Feb 83 | 01 Mar 83 | Yes | 302 | 334 | 356 | 392 | 418 | 319 | 17 |
| 83D00080 | 101 | 12 Feb 83 | 04 Mar 83 | Yes | 245 | 270 | 289 | * | 346 | 261 | 16 |
| 83D00097 | 101 | 12 Feb 83 | 04 Mar 83 | Yes | 282 | 319 | 320 | * | 423 | 336 | 54 |

* Weight not obtained.

Misdosed Animals

| MPP Dose | Maternal ID | Date Removed |
|---|---|---|
| 0 | 82D00716 | 26 Oct 82 |
| 0 | 83D00033 | 16 Feb 83 |
| 3.12 | 83D00074 | 19 Feb 83 |
| 1.25 | 83D00018 | 18 Feb 83 |
| 1.25 | 83D00022 | 16 Feb 83 |
| 1.25 | 83D00057 | 19 Feb 83 |
| 0.12 | 82D00737 | 25 Oct 82 |
| 0.12 | 83D00035 | 21 Feb 83 |
| 0.12 | 83D00094 | 23 Feb 83 |

Maternal Clinical Signs - Vehicle Animals

| Maternal ID | Study Day | Date | Signs |
|---|---|---|---|
| 82D00691 | 14 | 28 Oct 82 | Brief bleeding from mouth on introduction of gavage needle, not dosed |
| 82D00703 | 20 | 2 Nov 82 | Enlarged uterus, left horn filled with fluid at sacrifice |
| 83D00039 | 15 | 23 Feb 83 | Sound production |
| 83D00062 | 11 | 21 Feb 83 | Misdose, slight foaming at mouth |
| 83D00063 | 7 | 16 Feb 83 | Red stained nose |
| | 14 | 23 Feb 83 | Sound production |
| 83D00082 | 0 | 12 Feb 83 | Slight weight loss |

Maternal Clinical Signs - 3.12 mg/kg/day MPP Animals

| Maternal ID | Study Day | Date | Signs |
|---|---|---|---|
| 82D00696 | 9 | 22 Oct 82 | Gasping, salivation |
| 83D00010 | 0 | 9 Feb 83 | Bloody vaginal discharge |
| 83D00016 | 0 | 8 Feb 83 | Bloody vaginal discharge |
| | 9 | 17 Feb 83 | Inactive |
| | 15 | 23 Feb 83 | Sound production |
| 83D00020 | 6 | 14 Feb 83 | Blood in mouth during dosing |
| 83D00024 | 8 | 17 Feb 83 | Inactive |
| 83D00042 | 0 | 8 Feb 83 | Slight weight loss |
| 83D00044 | 7 | 16 Feb 83 | Yellow stained mouth |
| | 8 | 17 Feb 83 | Yellow stained mouth |
| 83D00047 | 6 | 16 Feb 83 | Misdose, vomiting |
| | 7 | 17 Feb 83 | Yellow stained mouth |
| | 13 | 23 Feb 83 | Red stained nose, sound production |
| | 14 | 24 Feb 83 | Convulsions, vomiting, inactive, sound production |
| | 15 | 25 Feb 83 | Red stained nose, sound production |
| 83D00050 | 8 | 17 Feb 83 | Inactive |
| 83D00059 | 0 | 8 Feb 83 | Slight weight loss |
| | 8 | 16 Feb 83 | Inactive |
| | 15 | 23 Feb 83 | Yellow stained perianal |
| | 16 | 24 Feb 83 | Blood on nose |
| 83D00101 | 12 | 23 Feb 83 | Yellow stained mouth, sound production |

Maternal Clinical Signs - 1.25 mg/kg/day MPP Animals

| Maternal ID | Study Day | Date | Signs |
|---|---|---|---|
| 82D00735 | 9 | 22 Oct 82 | Blood in mouth at dosing |
| 82D00740 | 20 | 4 Nov 82 | Yellow fluid filled mass in left axilla |
| 83D00003 | 12 | 24 Feb 83 | Inactive |
| 83D00029 | 8 | 17 Feb 83 | Bloody vaginal discharge, signs of abortion |
| | 9 | 18 Feb 83 | Clotted blood in vaginal area |
| | 14 | 23 Feb 83 | Bloody vaginal discharge, sound production, cyanosis |
| | 15 | 24 Feb 83 | Bloody vaginal discharge, sound production, inactive |
| | 16 | 25 Feb 83 | Sound production, cyanosis |
| | 17 | 26 Feb 83 | Inactive |
| 83D00031 | 7 | 17 Feb 83 | Inactive |
| 83D00032 | 13 | 23 Feb 83 | Mass in right axilla |
| | 20 | 2 Mar 83 | At sacrifice mass revealed granulomatous tissue |
| 83D00056 | 9 | 17 Feb 83 | Hunched posture |
| 83D00067 | 15 | 23 Feb 83 | Sound production |
| | 16 | 24 Feb 83 | Sharp weight loss |
| 83D00077 | 0 | 9 Feb 83 | Bloody vaginal discharge |
| | 20 | 1 Mar 83 | 3 bladder stones at sacrifice |

Maternal Clinical Signs - 0.12 mg/kg/day MPP Animals

| Maternal ID | Study Day | Date | Signs |
|---|---|---|---|
| 82D00686 | 14 | 27 Oct 82 | Received partial dose |
| 83D00011 | 0 | 11 Feb 83 | Bloody vaginal discharge |
| 83D00025 | 8 | 17 Feb 83 | Weight loss |
| | 15 | 24 Feb 83 | Ataxia, inactive |
| 83D00054 | 0 | 8 Feb 83 | Slight weight loss |
| | 12 | 20 Feb 83 | Sound production |
| 83D00078 | 8 | 17 Feb 83 | Ataxia |
| 83D00080 | 0 | 12 Feb 83 | Slight weight loss |
| 83D00097 | 6 | 18 Feb 83 | Red stained mouth, nose |
| | 7 | 19 Feb 83 | Red stained mouth |
| | 12 | 24 Feb 83 | Ataxia, inactive |

Individual Uterine and Litter Data - Vehicle Animals

| Maternal ID | Implantations | Resorptions | Resorp.% | ---- Number of Fetuses ---- Dead | Dead % | Live | Live % |
|---|---|---|---|---|---|---|---|
| 82D00682 | 14 | 5 | 36 | 0 | 0 | 9 | 64 |
| 82D00691 | 18 | 1 | 6 | 0 | 0 | 17 | 94 |
| 82D00698 | 14 | 0 | 0 | 0 | 0 | 14 | 100 |
| 82D00703 | 1 | 0 | 0 | 0 | 0 | 1 | 100 |
| 82D00719 | 16 | 1 | 6 | 0 | 0 | 15 | 94 |
| 82D00724 | 9 | 3 | 33 | 0 | 0 | 6 | 67 |
| 82D00743 | 15 | 3 | 20 | 0 | 0 | 12 | 80 |
| 82D00751 | 10 | 1 | 10 | 0 | 0 | 9 | 90 |
| 83D00001 | 13 | 4 | 31 | 0 | 0 | 9 | 69 |
| 83D00019 | 18 | 0 | 0 | 0 | 0 | 18 | 100 |
| 83D00039 | 7 | 0 | 0 | 0 | 0 | 7 | 100 |
| 83D00062 | 19 | 0 | 0 | 0 | 0 | 19 | 100 |
| 83D00063 | 15 | 1 | 7 | 0 | 0 | 14 | 93 |
| 83D00070 | 19 | 1 | 5 | 0 | 0 | 18 | 95 |
| 83D00076 | 18 | 1 | 6 | 0 | 0 | 17 | 94 |
| 83D00082 | 16 | 2 | 12 | 0 | 0 | 14 | 88 |
| 83D00096 | 18 | 2 | 11 | 0 | 0 | 16 | 89 |

Individual Uterine and Litter Data - 3.12 mg/kg/day MPP Animals

| Maternal ID | Implantations | Resorptions | Resorp.% | Number of Fetuses | | | |
|---|---|---|---|---|---|---|---|
| | | | | Dead | Dead % | Live | Live % |
| 82D00681 | 17 | 3 | 18 | 0 | 0 | 14 | 82 |
| 82D00696 | 15 | 2 | 13 | 0 | 0 | 13 | 87 |
| 82D00699 | 11 | 4 | 36 | 0 | 0 | 7 | 64 |
| 82D00704 | 17 | 0 | 0 | 0 | 0 | 17 | 100 |
| 82D00706 | 13 | 1 | 8 | 0 | 0 | 12 | 92 |
| 82D00723 | 17 | 1 | 6 | 0 | 0 | 16 | 94 |
| 82D00728 | 13 | 1 | 8 | 0 | 0 | 12 | 92 |
| 82D00734 | 12 | 0 | 0 | 0 | 0 | 12 | 100 |
| 82D00739 | 18 | 2 | 11 | 0 | 0 | 16 | 89 |
| 82D00750 | 16 | 0 | 0 | 0 | 0 | 16 | 100 |
| 82D00752 | 17 | 1 | 6 | 0 | 0 | 16 | 94 |
| 83D00010 | 16 | 1 | 6 | 0 | 0 | 15 | 94 |
| 83D00016 | 14 | 0 | 0 | 0 | 0 | 14 | 100 |
| 83D00020 | 18 | 0 | 0 | 0 | 0 | 18 | 100 |
| 83D00024 | 18 | 1 | 6 | 0 | 0 | 17 | 94 |
| 83D00042 | 18 | 2 | 11 | 0 | 0 | 16 | 89 |
| 83D00044 | 15 | 1 | 6 | 0 | 0 | 14 | 94 |
| 83D00047 | 16 | 2 | 12 | 0 | 0 | 14 | 88 |
| 83D00050 | 13 | 1 | 8 | 0 | 0 | 12 | 92 |
| 83D00059 | 18 | 1 | 6 | 0 | 0 | 17 | 94 |
| 83D00073 | 18 | 0 | 0 | 0 | 0 | 18 | 100 |
| 83D00101 | 17 | 8 | 47 | 0 | 0 | 9 | 53 |

## Individual Uterine and Litter Data - 1.25 mg/kg/day MPP Animals

| Maternal ID | Implantations | Resorptions | Resorp.% | Number of Fetuses: Dead | Dead % | Live | Live % |
|---|---|---|---|---|---|---|---|
| 82D00689 | 11 | 2 | 18 | 0 | 0 | 9 | 82 |
| 82D00697 | 17 | 0 | 0 | 0 | 0 | 17 | 100 |
| 82D00700 | 16 | 1 | 6 | 0 | 0 | 15 | 94 |
| 82D00710 | 15 | 2 | 13 | 0 | 0 | 13 | 87 |
| 82D00715 | 16 | 0 | 0 | 0 | 0 | 16 | 100 |
| 82D00731 | 16 | 0 | 0 | 0 | 0 | 16 | 100 |
| 82D00735 | 5 | 1 | 20 | 0 | 0 | 4 | 80 |
| 82D00740 | 11 | 4 | 36 | 0 | 0 | 7 | 64 |
| 82D00745 | 16 | 3 | 19 | 0 | 0 | 13 | 81 |
| 82D00763 | 14 | 2 | 14 | 0 | 0 | 12 | 86 |
| 83D00003 | 16 | 2 | 12 | 0 | 0 | 14 | 88 |
| 83D00014 | 8 | 3 | 38 | 0 | 0 | 5 | 62 |
| 83D00029 | 17 | 17 | 100 | 0 | 0 | 0 | 0 |
| 83D00031 | 5 | 0 | 0 | 0 | 0 | 5 | 100 |
| 83D00032 | 19 | 3 | 16 | 0 | 0 | 16 | 84 |
| 83D00037 | 19 | 0 | 0 | 0 | 0 | 19 | 100 |
| 83D00056 | 12 | 2 | 17 | 0 | 0 | 10 | 83 |
| 83D00060 | 17 | 2 | 12 | 0 | 0 | 15 | 88 |
| 83D00067 | 18 | 2 | 11 | 0 | 0 | 16 | 89 |
| 83D00077 | 17 | 1 | 6 | 0 | 0 | 16 | 94 |

Individual Uterine and Litter Data - 0.12 mg/kg/day MPP Animals

| Maternal ID | Implantations | Resorptions | Resorp.% | ---- Number of Fetuses ---- Dead | Dead % | Live | Live % |
|---|---|---|---|---|---|---|---|
| 82D00693 | 16 | 2 | 12 | 0 | 0 | 14 | 88 |
| 82D00714 | 16 | 1 | 6 | 0 | 0 | 15 | 94 |
| 82D00727 | 18 | 1 | 6 | 0 | 0 | 17 | 94 |
| 82D00729 | 13 | 1 | 8 | 0 | 0 | 12 | 92 |
| 82D00746 | 13 | 2 | 15 | 0 | 0 | 11 | 85 |
| 82D00764 | 6 | 0 | 0 | 0 | 0 | 6 | 100 |
| 83D00004 | 13 | 0 | 0 | 0 | 0 | 13 | 100 |
| 83D00011 | 13 | 0 | 0 | 0 | 0 | 13 | 100 |
| 83D00015 | 17 | 2 | 12 | 0 | 0 | 15 | 88 |
| 83D00023 | 13 | 1 | 8 | 0 | 0 | 12 | 92 |
| 83D00025 | 17 | 2 | 12 | 0 | 0 | 15 | 88 |
| 83D00030 | 17 | 0 | 0 | 0 | 0 | 17 | 100 |
| 83D00034 | 18 | 1 | 6 | 0 | 0 | 17 | 94 |
| 83D00038 | 16 | 3 | 19 | 0 | 0 | 13 | 81 |
| 83D00043 | 12 | 1 | 8 | 0 | 0 | 11 | 92 |
| 83D00054 | 13 | 2 | 15 | 0 | 0 | 11 | 85 |
| 83D00069 | 17 | 1 | 6 | 0 | 0 | 16 | 94 |
| 83D00075 | 10 | 0 | 0 | 0 | 0 | 10 | 100 |
| 83D00078 | 18 | 1 | 6 | 0 | 0 | 17 | 94 |
| 83D00080 | 18 | 3 | 16 | 1 | 6 | 14 | 78 |
| 83D00097 | 14 | 3 | 21 | 0 | 0 | 11 | 79 |

Fetal Sex and Weight - Vehicle Animals

| Maternal ID | Sex | | | Mean Weight(g) ±S.D. | | |
|---|---|---|---|---|---|---|
| | Males | Females | Males(%) | Fetal | Males | Females |
| 82D00682 | 7 | 2 | 78 | 6.16±.26 | 6.21±.27 | 5.95±.07 |
| 82D00691 | 9 | 8 | 53 | 3.66±.57 | 3.98±.11 | 3.31±.68 |
| 82D00698 | 6 | 8 | 43 | 3.55±.25 | 3.77±.12 | 3.39±.19 |
| 82D00703 | 1 | 0 | 100 | 6.40 | 6.40 | |
| 82D00719 | 11 | 4 | 73 | 4.47±.35 | 4.57±.20 | 4.18±.53 |
| 82D00724 | 4 | 2 | 67 | 6.27±.29 | 6.40±.26 | 6.00±.14 |
| 82D00743 | 6 | 6 | 50 | 4.18±.28 | 4.27±.27 | 4.08±.28 |
| 82D00751 | 2 | 7 | 22 | 3.79±.33 | 4.20±.00 | 3.67±.27 |
| 83D00001 | 4 | 5 | 44 | 4.16±.14 | 4.20±.16 | 4.12±.13 |
| 83D00019 | 11 | 7 | 61 | 4.09±.22 | 4.20±.20 | 3.93±.14 |
| 83D00039 | 5 | 2 | 71 | 4.19±.27 | 4.18±.33 | 4.20±.14 |
| 83D00062 | 12 | 7 | 63 | 3.22±.27 | 3.25±.22 | 3.16±.36 |
| 83D00063 | 7 | 7 | 50 | 3.83±.50 | 3.96±.54 | 3.70±.46 |
| 83D00070 | 8 | 10 | 44 | 3.57±.20 | 3.70±.22 | 3.47±.12 |
| 83D00076 | 11 | 6 | 65 | 3.88±.19 | 3.96±.16 | 3.73±.15 |
| 83D00082 | 7 | 7 | 50 | 3.74±.44 | 3.96±.11 | 3.51±.54 |
| 83D00096 | 7 | 9 | 44 | 3.49±.15 | 3.43±.17 | 3.56±.10 |

Fetal Sex and Weight - 3.12 mg/kg/day MPP Animals

| Maternal ID | Sex | | | Mean Weight(g) ± S.D. | | |
|---|---|---|---|---|---|---|
| | Males | Females | Males(%) | Fetal | Males | Females |
| 82D00681 | 8 | 6 | 57 | 5.91±.32 | 6.06±.24 | 5.70±.31 |
| 82D00696 | 3 | 10 | 23 | 3.66±.28 | 3.47±.40 | 3.72±.22 |
| 82D00699 | 4 | 3 | 57 | 3.93±.13 | 3.98±.13 | 3.87±.40 |
| 82D00704 | 9 | 8 | 53 | 3.83±.31 | 4.02±.22 | 3.61±.26 |
| 82D00706 | 7 | 5 | 58 | 4.10±.41 | 4.27±.40 | 3.86±.31 |
| 82D00723 | 6 | 10 | 37 | 3.93±.30 | 3.98±.39 | 3.89±.24 |
| 82D00728 | 9 | 3 | 75 | 3.93±.30 | 3.93±.35 | 3.90±.10 |
| 82D00734 | 7 | 5 | 58 | 6.02±.24 | 6.10±.26 | 5.90±.16 |
| 82D00739 | 9 | 7 | 56 | 4.55±.34 | 4.71±.27 | 4.34±.34 |
| 82D00750 | 10 | 6 | 62 | 3.61±.44 | 3.81±.11 | 3.28±.59 |
| 82D00752 | 8 | 8 | 50 | 4.28±.18 | 4.25±.18 | 4.30±.19 |
| 83D00010 | 12 | 3 | 80 | 3.78±.19 | 3.81±.20 | 3.67±.12 |
| 83D00016 | 9 | 5 | 64 | 3.94±.15 | 4.01±.15 | 3.80±.00 |
| 83D00020 | 8 | 10 | 44 | 3.44±.29 | 3.45±.26 | 3.43±.32 |
| 83D00024 | 6 | 11 | 35 | 3.55±.17 | 3.65±.08 | 3.49±.18 |
| 83D00042 | 10 | 6 | 62 | 3.78±.23 | 3.77±.28 | 3.80±.14 |
| 83D00044 | 6 | 8 | 43 | 3.66±.13 | 3.70±.13 | 3.63±.14 |
| 83D00047 | 7 | 7 | 50 | 3.81±.24 | 3.94±.26 | 3.73±.12 |
| 83D00050 | 9 | 3 | 75 | 3.73±.44 | 3.76±.52 | 3.67±.06 |
| 83D00059 | 6 | 11 | 35 | 5.87±.18 | 5.93±.22 | 5.84±.14 |
| 83D00073 | 10 | 8 | 56 | 3.32±.24 | 3.36±.29 | 3.28±.18 |
| 83D00101 | 5 | 4 | 56 | 3.31±.26 | 3.48±.22 | 3.10±.08 |

Fetal Sex and Weight - 1.25 mg/kg/day MPP Animals

| Maternal ID | Sex | | | Mean Weight(g) ± S.D. | | |
|---|---|---|---|---|---|---|
| | Males | Females | Males(%) | Fetal | Males | Females |
| 82D00689 | 3 | 6 | 33 | 3.89±.27 | 4.00±.20 | 3.83±.30 |
| 82D00697 | 10 | 7 | 58 | 3.81±.18 | 3.88±.12 | 3.70±.21 |
| 82D00700 | 11 | 4 | 73 | 5.56±.23 | 5.65±.18 | 5.30±.08 |
| 82D00710 | 6 | 7 | 46 | 4.02±.19 | 4.15±.12 | 3.90±.16 |
| 82D00715 | 9 | 7 | 56 | 3.90±.19 | 3.84±.32 | 3.97±.14 |
| 82D00731 | 11 | 5 | 69 | 3.54±.25 | 3.58±.26 | 3.46±.23 |
| 82D00735 | 1 | 3 | 25 | 4.35±.38 | 4.60 | 4.27±.42 |
| 82D00740 | 5 | 2 | 71 | 3.39±.26 | 3.36±.26 | 3.45±.35 |
| 82D00745 | 10 | 3 | 77 | * | * | * |
| 82D00763 | 3 | 9 | 25 | 3.30±.77 | 2.73±1.4 | 3.49±.40 |
| 83D00003 | 8 | 6 | 57 | 3.41±.26 | 3.48±.27 | 3.32±.25 |
| 83D00014 | 0 | 5 | 0 | 4.06±.40 | | 4.06±.40 |
| 83D00031 | 1 | 4 | 20 | 3.92±.41 | 4.10 | 3.88±.46 |
| 83D00032 | 7 | 9 | 44 | 3.81±.29 | 3.99±.17 | 3.68±.30 |
| 83D00037 | 12 | 7 | 63 | 3.93±.20 | 3.98±.18 | 3.84±.21 |
| 83D00056 | 6 | 4 | 60 | 5.95±.50 | 6.23±.12 | 5.52±.57 |
| 83D00060 | 6 | 9 | 40 | 3.73±.30 | 3.90±.17 | 3.61±.32 |
| 83D00067 | 8 | 8 | 50 | 4.88±.27 | 4.96±.21 | 4.80±.31 |
| 83D00077 | 8 | 8 | 50 | 3.25±.54 | 3.44±.45 | 3.64±.23 |

* Fetuses not weighed.

Fetal Sex and Weight - 0.12 mg/kg/day MPP Animals

| Maternal ID | Sex | | | Mean Weight(g) ± S.D. | | |
|---|---|---|---|---|---|---|
| | Males | Females | Males(%) | Fetal | Males | Females |
| 82D00693 | 8 | 6 | 57 | 3.90±.25 | 4.05±.18 | 3.70±.19 |
| 82D00714 | 8 | 7 | 53 | 5.75±.19 | 5.80±.19 | 5.69±.20 |
| 82D00727 | 10 | 7 | 59 | 4.37±.16 | 4.40±.14 | 4.33±.18 |
| 82D00729 | 6 | 6 | 50 | 3.86±.28 | 4.02±.32 | 3.70±.13 |
| 82D00746 | 4 | 7 | 36 | 4.49±.39 | 4.73±.13 | 4.39±.44 |
| 82D00764 | 5 | 1 | 83 | 3.90±.32 | 3.86±.34 | 4.10 |
| 83D00004 | 8 | 5 | 62 | 3.70±.26 | 3.72±.27 | 3.66±.25 |
| 83D00011 | 4 | 9 | 31 | 3.73±.16 | 3.88±.15 | 3.67±.12 |
| 83D00015 | 9 | 6 | 60 | 3.87±.23 | 4.01±.10 | 3.67±.22 |
| 83D00023 | 7 | 5 | 58 | 4.08±.35 | 4.04±.45 | 4.14±.11 |
| 83D00025 | 8 | 7 | 53 | 4.07±.27 | 4.14±.22 | 3.99±.32 |
| 83D00030 | 11 | 6 | 65 | 3.21±.18 | 3.24±.20 | 3.15±.14 |
| 83D00034 | 6 | 11 | 35 | 3.77±.20 | 3.93±.10 | 3.68±.19 |
| 83D00038 | 8 | 5 | 62 | 5.70±.40 | 5.84±.35 | 5.48±.41 |
| 83D00043 | 1 | 10 | 9 | 3.75±.20 | 3.80 | 3.74±.21 |
| 83D00054 | 5 | 6 | 45 | 7.44±.55 | 7.74±.20 | 7.18±.64 |
| 83D00069 | 9 | 7 | 56 | 3.76±.17 | 3.80±.13 | 3.71±.21 |
| 83D00075 | 6 | 4 | 60 | 4.24±.25 | 4.30±.17 | 4.15±.34 |
| 83D00078 | 9 | 8 | 53 | 3.44±.17 | 3.48±.18 | 3.39±.17 |
| 83D00080 | 6 | 8 | 43 | 3.27±.26 | 3.50±.14 | 3.10±.19 |
| 83D00097 | 2 | 9 | 18 | 4.73±.38 | 5.25±.21 | 4.61±.31 |

Description and Incidence of Fetal External Examination Findings - Vehicle Animals

| Maternal ID | No.* | Variants | | Anomalies | |
|---|---|---|---|---|---|
| | | No.† | No. and Description of Each Variant | No.§ | No. and Description of Each Anomaly |
| 82D00682 | 9 | 0 | | 0 | |
| 82D00691 | 17 | 0 | | 0 | |
| 82D00698 | 14 | 0 | | 0 | |
| 82D00703 | 1 | 0 | | 1 | 1 Domed cranium<br>1 Protruding tongue |
| 82D00719 | 15 | 0 | | 0 | |
| 82D00724 | 6 | 0 | | 0 | |
| 82D00743 | 12 | 0 | | 0 | |
| 82D00751 | 9 | 0 | | 0 | |
| 83D00001 | 9 | 0 | | 0 | |
| 83D00019 | 18 | 0 | | 0 | |
| 83D00039 | 7 | 0 | | 0 | |
| 83D00062 | 19 | 0 | | 0 | |
| 83D00063 | 14 | 0 | | 0 | |
| 83D00070 | 18 | 0 | | 0 | |
| 83D00076 | 17 | 0 | | 0 | |
| 83D00082 | 14 | 0 | | 0 | |
| 83D00096 | 16 | 0 | | 0 | |

* Number of fetuses examined.
† Number of fetuses with variants.
§ Number of fetuses with anomalies.

Description and Incidence of Fetal External Examination Findings - 3.12 mg/kg/day MPP Animals

| Maternal ID | Variants | | | Anomalies | |
|---|---|---|---|---|---|
| | No.* | No.† | No. and Description of Each Variant | No.§ | No. and Description of Each Anomaly |
| 82D00681 | 14 | 0 | | 0 | |
| 82D00696 | 13 | 0 | | 0 | |
| 82D00699 | 7 | 0 | | 0 | |
| 82D00704 | 17 | 0 | | 0 | |
| 82D00706 | 12 | 0 | | 0 | |
| 82D00723 | 16 | 0 | | 0 | |
| 82D00728 | 12 | 0 | | 0 | |
| 82D00734 | 12 | 0 | | 0 | |
| 82D00739 | 16 | 0 | | 0 | |
| 82D00750 | 16 | 1 | 1 Hemorrhage on cranium | 0 | |
| 82D00752 | 16 | 0 | | 0 | |
| 83D00010 | 15 | 0 | | 0 | |
| 83D00016 | 14 | 0 | | 0 | |
| 83D00020 | 18 | 0 | | 0 | |
| 83D00024 | 17 | 0 | | 0 | |
| 83D00042 | 16 | 0 | | 0 | |
| 83D00044 | 14 | 0 | | 0 | |
| 83D00047 | 14 | 0 | | 0 | |
| 83D00050 | 12 | 0 | | 0 | |
| 83D00059 | 17 | 0 | | 0 | |
| 83D00073 | 18 | 0 | | 0 | |
| 83D00101 | 9 | 0 | | 0 | |

* Number of fetuses examined.
† Number of fetuses with variants.
§ Number of fetuses with anomalies.

Description and Incidence of Fetal External Examination Findings - 1.25 mg/kg/day MPP Animals

| Maternal ID | No.* | Variants | | Anomalies | |
|---|---|---|---|---|---|
| | | No.† | No. and Description of Each Variant | No.§ | No. and Description of Each Anomaly |
| 82D00689 | 9 | 0 | | 0 | |
| 82D00697 | 17 | 0 | | 0 | |
| 82D00700 | 15 | 0 | | 0 | |
| 82D00710 | 13 | 0 | | 0 | |
| 82D00715 | 16 | 0 | | 0 | |
| 82D00731 | 16 | 0 | | 0 | |
| 82D00735 | 4 | 0 | | 0 | |
| 82D00740 | 7 | 0 | | 0 | |
| 82D00745 | 13 | 0 | | 0 | |
| 82D00763 | 12 | 0 | | 0 | |
| 83D00003 | 14 | 0 | | 0 | |
| 83D00014 | 5 | 0 | | 0 | |
| 83D00031 | 5 | 0 | | 0 | |
| 83D00032 | 16 | 0 | | 0 | |
| 83D00037 | 19 | 0 | | 0 | |
| 83D00056 | 10 | 0 | | 0 | |
| 83D00060 | 15 | 0 | | 0 | |
| 83D00067 | 16 | 0 | | 0 | |
| 83D00077 | 16 | 0 | | 1 | 1 Cleft palate |

* Number of fetuses examined.
† Number of fetuses with variants.
§ Number of fetuses with anomalies.

Description and Incidence of Fetal External Examination Findings - 0.12 mg/kg/day MPP Animals

| Maternal ID | No.* | Variants | | Anomalies | |
|---|---|---|---|---|---|
| | | No.† | No. and Description of Each Variant | No.§ | No. and Description of Each Anomaly |
| 82D00693 | 14 | 0 | | 0 | |
| 82D00714 | 15 | 0 | | 0 | |
| 82D00727 | 17 | 0 | | 0 | |
| 82D00729 | 12 | 0 | | 0 | |
| 82D00746 | 11 | 0 | | 0 | |
| 82D00764 | 6 | 0 | | 0 | |
| 83D00004 | 13 | 0 | | 0 | |
| 83D00011 | 13 | 0 | | 0 | |
| 83D00015 | 15 | 0 | | 0 | |
| 83D00023 | 12 | 0 | | 0 | |
| 83D00025 | 15 | 0 | | 0 | |
| 83D00030 | 17 | 0 | | 0 | |
| 83D00034 | 17 | 0 | | 0 | |
| 83D00038 | 13 | 0 | | 0 | |
| 83D00043 | 11 | 0 | | 0 | |
| 83D00054 | 11 | 0 | | 0 | |
| 83D00069 | 16 | 0 | | 0 | |
| 83D00075 | 10 | 0 | | 0 | |
| 83D00078 | 17 | 0 | | 0 | |
| 83D00080 | 11 | 0 | | 0 | |
| 83D00097 | 11 | 0 | | 0 | |

* Number of fetuses examined.
† Number of fetuses with variants.
§ Number of fetuses with anomalies.

Description and Incidence of Fetal Visceral Examination Findings - Vehicle Animals

| Maternal ID | No.* | Variants | | Anomalies | |
|---|---|---|---|---|---|
| | | No.† | No. and Description of Each Variant | No.§ | No. and Description of Each Anomaly |
| 82D00682 | 4 | 0 | | 0 | |
| 82D00691 | 8 | 1 | 1 Dilated brain ventricles | 0 | |
| 82D00698 | 7 | 0 | | 0 | |
| 82D00719 | 7 | 0 | | 0 | |
| 82D00724 | 3 | 0 | | 0 | |
| 82D00743 | 6 | 2 | 1 Dilated renal pelvis<br>1 Small kidney | 0 | |
| 82D00751 | 5 | 2 | 1 Dilated renal pelvis<br>1 Small lens | 0 | |
| 83D00001 | 4 | 0 | | 0 | |
| 83D00019 | 9 | 4 | 1 Cerebral hemorrhage<br>3 Dilated renal pelvis | 0 | |
| 83D00039 | 3 | 0 | | 0 | |
| 83D00062 | 10 | 5 | 5 Small kidney | 0 | |
| 83D00063 | 7 | 0 | | 0 | |
| 83D00070 | 9 | 1 | 1 Dilated renal pelvis | 0 | |
| 83D00076 | 8 | 0 | | 0 | |
| 83D00082 | 7 | 5 | 5 Dilated renal pelvis | 0 | |
| 83D00096 | 8 | 2 | 2 Cerebral hemorrhage | 0 | |

* Number of fetuses examined.
† Number of fetuses with variants.
§ Number of fetuses with anomalies.

Description and Incidence of Fetal Visceral Examination Findings - 3.12 mg/kg/day MPP Animals

| Maternal ID | No.* | Variants | | Anomalies | |
|---|---|---|---|---|---|
| | | No.† | No. and Description of Each Variant | No.§ | No. and Description of Each Anomaly |
| 82D00681 | 7 | 1 | 1 Dilated renal pelvis | 0 | |
| 82D00696 | 6 | 0 | | 0 | |
| 82D00699 | 3 | 0 | | 0 | |
| 82D00704 | 8 | 0 | | 0 | |
| 82D00706 | 6 | 0 | | 0 | |
| 82D00723 | 8 | 0 | | 0 | |
| 82D00728 | 6 | 0 | | 0 | |
| 82D00734 | 6 | 0 | | 0 | |
| 82D00739 | 8 | 0 | | 0 | |
| 82D00750 | 8 | 0 | | 0 | |
| 82D00752 | 8 | 0 | | 0 | |
| 83D00010 | 7 | 2 | 2 Dilated renal pelvis | 0 | |
| 83D00016 | 7 | 0 | | 0 | |
| 83D00020 | 9 | 0 | | 0 | |
| 83D00024 | 8 | 0 | | 0 | |
| 83D00042 | 8 | 0 | | 0 | |
| 83D00044 | 7 | 1 | 1 Dilated renal pelvis | 0 | |
| 83D00047 | 7 | 2 | 1 Dilated renal pelvis<br>1 Small kidney | 0 | |
| 83D00050 | 6 | 2 | 2 Dilated renal pelvis | 0 | |
| 83D00059 | 8 | 1 | 1 Dilated renal pelvis | 0 | |
| 83D00073 | 9 | 0 | | 0 | |
| 83D00101 | 4 | 1 | 1 Dilated renal pelvis | 0 | |

* Number of fetuses examined.
† Number of fetuses with variants.
§ Number of fetuses with anomalies.

Description and Incidence of Fetal Visceral Examination Findings - 1.25 mg/kg/day MPP Animals

| Maternal ID | No.* | Variants | | Anomalies | |
|---|---|---|---|---|---|
| | | No.† | No. and Description of Each Variant | No.§ | No. and Description of Each Anomaly |
| 82D00689 | 4 | 0 | | 0 | |
| 82D00697 | 8 | 0 | | 0 | |
| 82D00700 | 7 | 0 | | 0 | |
| 82D00710 | 6 | 5 | 5 Dilated renal pelvis | 0 | |
| 82D00715 | 8 | 0 | | 0 | |
| 82D00731 | 8 | 1 | 1 Small kidney | 0 | |
| 82D00735 | 2 | 0 | | 0 | |
| 82D00740 | 3 | 0 | | 0 | |
| 82D00745 | 6 | 0 | | 0 | |
| 82D00763 | 6 | 1 | 1 Small kidney | 0 | |
| 83D00003 | 7 | 0 | | 0 | |
| 83D00014 | 2 | 0 | | 0 | |
| 83D00031 | 2 | 1 | 1 Dilated renal pelvis | 0 | |
| 83D00032 | 8 | 0 | | 0 | |
| 83D00037 | 9 | 0 | | 0 | |
| 83D00056 | 5 | 1 | 1 Dilated renal pelvis | 0 | |
| 83D00060 | 7 | 0 | | 0 | |
| 83D00067 | 7 | 0 | | 0 | |
| 83D00077 | 8 | 2 | 1 Dilated renal pelvis<br>1 Microphthalmia | 1 | 1 Cleft palate |

* Number of fetuses examined.
† Number of fetuses with variants.
§ Number of fetuses with anomalies.

Description and Incidence of Fetal Visceral Examination Findings - 0.12 mg/kg/day MPP Animals

| Maternal ID | No.* | Variants | | Anomalies | |
|---|---|---|---|---|---|
| | | No.† | No. and Description of Each Variant | No.§ | No. and Description of Each Anomaly |
| 82D00693 | 7 | 1 | 1 Dilated renal pelvis | 0 | |
| 82D00714 | 8 | 0 | | 0 | |
| 82D00727 | 8 | 0 | | 0 | |
| 82D00729 | 6 | 1 | 1 Dilated renal pelvis | 0 | |
| 82D00746 | 5 | 2 | 2 Dilated renal pelvis | 0 | |
| 82D00764 | 3 | 0 | | 0 | |
| 83D00004 | 6 | 1 | 1 Dilated renal pelvis | 0 | |
| 83D00011 | 6 | 1 | 1 Dilated renal pelvis | 0 | |
| 83D00015 | 7 | 2 | 2 Cerebral hemorrhage<br>1 Dilated renal pelvis | 0 | |
| 83D00023 | 6 | 1 | 1 Dilated renal pelvis | 0 | |
| 83D00025 | 7 | 0 | | 0 | |
| 83D00030 | 8 | 5 | 5 Dilated renal pelvis | 0 | |
| 83D00034 | 8 | 0 | | 0 | |
| 83D00038 | 6 | 0 | | 0 | |
| 83D00043 | 5 | 0 | | 0 | |
| 83D00054 | 5 | 2 | 2 Dilated renal pelvis | 0 | |
| 83D00069 | 8 | 0 | | 0 | |
| 83D00075 | 5 | 0 | | 0 | |
| 83D00078 | 8 | 2 | 2 Dilated renal pelvis | 0 | |
| 83D00080 | 7 | 1 | 1 Dilated renal pelvis | 0 | |
| 83D00097 | 5 | 0 | | 0 | |

* Number of fetuses examined.
† Number of fetuses with variants.
§ Number of fetuses with anomalies.

Description and Incidence of Fetal Skeletal Examination Findings - Vehicle Animals

| Maternal ID | No.* | Variants No.† | Variants No. and Description of Each Variant | Anomalies No.§ | Anomalies No. and Description of Each Anomaly |
|---|---|---|---|---|---|
| 82D00682 | 5 | 0 | | 0 | |
| 82D00691 | 9 | 3 | Incomplete ossification:<br>3 Cranium<br>1 Wavy ribs | 0 | |
| 82D00698 | 7 | 0 | | 0 | |
| 82D00703 | 1 | 1 | 1 Large orbit | 1 | 1 Domed cranium<br>1 Short maxilla/long mandible |
| 82D00719 | 8 | 0 | | 0 | |
| 82D00724 | 3 | 0 | | 0 | |
| 82D00743 | 6 | 5 | Incomplete ossification:<br>5 Cranium | 0 | |
| 82D00751 | 4 | 0 | | 0 | |
| 83D00001 | 5 | 2 | Incomplete ossification:<br>2 Cranium<br>1 Wavy ribs | 0 | |
| 83D00019 | 9 | 2 | Incomplete ossification:<br>2 Vertebral centra | 0 | |
| 83D00039 | 4 | 0 | | 0 | |
| 83D00062 | 9 | 3 | Incomplete ossification:<br>1 Cranium<br>3 Vertebral centra | 0 | |

* Number of fetuses examined.
† Number of fetuses with variants.
§ Number of fetuses with anomalies.

Description and Incidence of Fetal Skeletal Examination Findings - Vehicle Animals

| Maternal ID | No.* | Variants | | Anomalies | |
|---|---|---|---|---|---|
| | | No.† | No. and Description of Each Variant | No.§ | No. and Description of Each Anomaly |
| 83D00063 | 7 | 1 | Incomplete ossification:<br>1 Cranium | 0 | |
| 83D00070 | 9 | 1 | Incomplete ossification:<br>1 Vertebral centra | 0 | |
| 83D00076 | 9 | 0 | | 0 | |
| 83D00082 | 7 | 0 | | 0 | |
| 83D00096 | 8 | 3 | Incomplete ossification:<br>2 Cranium<br>1 Vertebral centra | 0 | |

* Number of fetuses examined.
† Number of fetuses with variants.
§ Number of fetuses with anomalies.

Description and Incidence of Fetal Skeletal Examination Findings - 3.12 mg/kg/day MPP Animals

| Maternal ID | No.* | Variants No.† | Variants No. and Description of Each Variant | Anomalies No.§ | Anomalies No. and Description of Each Anomaly |
|---|---|---|---|---|---|
| 82D00681 | 7 | 1 | 1 Lumbar rib | 0 | |
| 82D00696 | 7 | 1 | 1 Lumbar rib | 0 | |
| 82D00699 | 4 | 0 | | 0 | |
| 82D00704 | 9 | 2 | Incomplete ossification:<br>1 Vertebral centra<br>1 Lumbar rib | 0 | |
| 82D00706 | 6 | 1 | Incomplete ossification:<br>1 Cranium | 0 | |
| 82D00723 | 8 | 3 | Incomplete ossification:<br>1 Vertebral centra<br>1 Cranium<br>2 Lumbar rib | 0 | |
| 82D00728 | 6 | 1 | Incomplete ossification:<br>1 Vertebral centra | 0 | |
| 82D00734 | 6 | 0 | | 0 | |
| 82D00739 | 8 | 0 | | 0 | |
| 82D00750 | 8 | 4 | Incomplete ossification:<br>2 Cranium<br>1 Vertebral centra<br>1 Lumbar rib<br>1 Wavy ribs | 0 | |
| 82D00752 | 8 | 3 | Incomplete ossification:<br>3 Cranium<br>1 Wavy ribs | 0 | |

* Number of fetuses examined.
† Number of fetuses with variants.
§ Number of fetuses with anomalies.

Description and Incidence of Fetal Skeletal Examination Findings - 3.12 mg/kg/day MPP Animals

| Maternal ID | Variants | | | Anomalies | |
|---|---|---|---|---|---|
| | No.* | No.† | No. and Description of Each Variant | No.§ | No. and Description of Each Anomaly |
| 83D00010 | 8 | 3 | Incomplete ossification:<br>2 Cranium<br>1 Wavy ribs | 0 | |
| 83D00016 | 7 | 0 | | 0 | |
| 83D00020 | 9 | 3 | Incomplete ossification:<br>3 Cranium | 0 | |
| 83D00024 | 9 | 1 | Incomplete ossification:<br>1 Cranium | 0 | |
| 83D00042 | 8 | 0 | | 0 | |
| 83D00044 | 7 | 0 | | 0 | |
| 83D00047 | 7 | 1 | Incomplete ossification:<br>1 Cranium | 0 | |
| 83D00050 | 6 | 1 | Incomplete ossification:<br>1 Vertebral centra | 0 | |
| 83D00059 | 9 | 0 | | 0 | |
| 83D00073 | 9 | 1 | Incomplete ossification:<br>1 Cranium<br>1 Vertebral centra<br>1 Pelvis | 0 | |
| 83D00101 | 5 | 2 | Incomplete ossification:<br>2 Vertebral centra | 0 | |

* Number of fetuses examined.
† Number of fetuses with variants.
§ Number of fetuses with anomalies.

Description and Incidence of Fetal Skeletal Examination Findings - 1.25 mg/kg/day MPP Animals

| Maternal ID | No.* | Variants | | Anomalies | |
|---|---|---|---|---|---|
| | | No.† | No. and Description of Each Variant | No.§ | No. and Description of Each Anomaly |
| 82D00689 | 5 | 2 | Incomplete ossification:<br>2 Vertebral centra | 0 | |
| 82D00697 | 9 | 3 | Incomplete ossification:<br>1 Cranium<br>1 Vertebral centra<br>1 Lumbar rib | 0 | |
| 82D00700 | 8 | 0 | | 0 | |
| 82D00710 | 7 | 2 | Incomplete ossification:<br>1 Cranium<br>1 Lumbar rib | 0 | |
| 82D00715 | 8 | 1 | Incomplete ossification:<br>1 Vertebral centra | 0 | |
| 82D00731 | 8 | 0 | | 0 | |
| 82D00735 | 2 | 1 | 1 Lumbar rib | 0 | |
| 82D00740 | 4 | 0 | | 0 | |
| 82D00745 | 7 | 4 | 4 Lumbar rib | 0 | |
| 82D00763 | 6 | 1 | Incomplete ossification:<br>1 Cranium | 0 | |
| 83D00003 | 7 | 0 | | 0 | |
| 83D00014 | 3 | 1 | Incomplete ossification:<br>1 Vertebral centra | 0 | |

* Number of fetuses examined.
† Number of fetuses with variants.
§ Number of fetuses with anomalies.

Description and Incidence of Fetal Skeletal Examination Findings - 1.25 mg/kg/day MPP Animals

| Maternal ID | No.* | Variants | | Anomalies | |
|---|---|---|---|---|---|
| | | No.† | No. and Description of Each Variant | No.§ | No. and Description of Each Anomaly |
| 83D00031 | 3 | 2 | Incomplete ossification:<br>2 Vertebral centra<br>1 Lumbar rib | 0 | |
| 83D00032 | 8 | 4 | Incomplete ossification:<br>3 Cranium<br>2 Vertebral centra | 0 | |
| 83D00037 | 10 | 0 | | 0 | |
| 83D00056 | 5 | 0 | | 0 | |
| 83D00060 | 8 | 0 | | 0 | |
| 83D00067 | 9 | 0 | | 0 | |
| 83D00077 | 8 | 3 | Incomplete ossification:<br>1 Vertebral centra<br>2 Pelvis | 0 | |

* Number of fetuses examined.
† Number of fetuses with variants.
§ Number of fetuses with anomalies.

Description and Incidence of Fetal Skeletal Examination Findings - 0.12 mg/kg/day MPP Animals

| Maternal ID | No.* | Variants | | Anomalies | |
|---|---|---|---|---|---|
| | | No.† | No. and Description of Each Variant | No.§ | No. and Description of Each Anomaly |
| 82D00693 | 7 | 3 | Incomplete ossification:<br>3 Vertebral centra | 0 | |
| 82D00714 | 7 | 0 | | 0 | |
| 82D00727 | 9 | 0 | | 0 | |
| 82D00729 | 6 | 0 | | 0 | |
| 82D00746 | 6 | 1 | Incomplete ossification:<br>1 Vertebral centra | 0 | |
| 82D00764 | 3 | 0 | | 0 | |
| 83D00004 | 7 | 3 | Incomplete ossification:<br>2 Cranium<br>1 Vertebral centra | 0 | |
| 83D00011 | 7 | 2 | Incomplete ossification:<br>2 Vertebral centra | 0 | |
| 83D00015 | 8 | 2 | Incomplete ossification:<br>2 Vertebral centra | 0 | |
| 83D00023 | 6 | 0 | | 0 | |
| 83D00025 | 8 | 0 | | 0 | |
| 83D00030 | 9 | 0 | | 0 | |

* Number of fetuses examined.
† Number of fetuses with variants.
§ Number of fetuses with anomalies.

Description and Incidence of Fetal Skeletal Examination Findings - 0.12 mg/kg/day MPP Animals

| Maternal ID | No.* | Variants | | Anomalies | |
|---|---|---|---|---|---|
| | | No.† | No. and Description of Each Variant | No.§ | No. and Description of Each Anomaly |
| 83D00034 | 9 | 2 | Incomplete ossification:<br>2 Cranium | 0 | |
| 83D00038 | 7 | 2 | Incomplete ossification:<br>2 Vertebral centra | 0 | |
| 83D00043 | 6 | 1 | 1 Short rib | 0 | |
| 83D00054 | 5‡ | 0 | | 0 | |
| 83D00069 | 8 | 4 | Incomplete ossification:<br>4 Cranium<br>Sternebrae:<br>1 Fewer than 3 ossified | 0 | |
| 83D00075 | 5 | 0 | | 0 | |
| 83D00078 | 9 | 0 | | 0 | |
| 83D00080 | 7 | 0 | | 0 | |
| 83D00097 | 6 | 0 | | 0 | |

* Number of fetuses examined.
† Number of fetuses with variants.
§ Number of fetuses with anomalies.
‡One fetus lost during skeletal staining process.

Incidence of External, Visceral, and Skeletal Examination Findings - Vehicle Animals

| Maternal ID | External | | | | | Visceral | | | | | Skeletal | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number Examined | Anomalies No. | % | Variants No. | % | Number Examined | Anomalies No. | % | Variants No. | % | Number Examined | Anomalies No. | % | Variants No. | % |
| 82D00682 | 9 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 |
| 82D00691 | 17 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 1 | 13 | 9 | 0 | 0 | 3 | 33 |
| 82D00698 | 14 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 |
| 82D00703 | 1 | 1 | 100 | 0 | 0 | - | - | - | - | - | 1 | 1 | 100 | 1 | 100 |
| 82D00719 | 15 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 |
| 82D00724 | 6 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| 82D00743 | 12 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 2 | 33 | 6 | 0 | 0 | 5 | 83 |
| 82D00751 | 9 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 2 | 40 | 4 | 0 | 0 | 0 | 0 |
| 83D00001 | 9 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 2 | 40 |
| 83D00019 | 18 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 4 | 44 | 9 | 0 | 0 | 2 | 22 |
| 83D00039 | 7 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 |
| 83D00062 | 19 | 0 | 0 | 0 | 0 | 10 | 0 | 0 | 5 | 50 | 9 | 0 | 0 | 3 | 33 |
| 83D00063 | 14 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 1 | 14 |
| 83D00070 | 18 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 1 | 11 | 9 | 0 | 0 | 1 | 11 |
| 83D00076 | 17 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 0 |
| 83D00082 | 14 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 5 | 71 | 7 | 0 | 0 | 0 | 0 |
| 83D00096 | 16 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 2 | 25 | 8 | 0 | 0 | 3 | 38 |

Incidence of External, Visceral, and Skeletal Examination Findings - 3.12 mg/kg/day MPP Animals

| Maternal ID | External | | | | | Visceral | | | | | Skeletal | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number Examined | Anomalies No. | % | Variants No. | % | Number Examined | Anomalies No. | % | Variants No. | % | Number Examined | Anomalies No. | % | Variants No. | % |
| 82D00681 | 14 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 1 | 14 | 7 | 0 | 0 | 1 | 14 |
| 82D00696 | 13 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 1 | 14 |
| 82D00699 | 7 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 |
| 82D00704 | 17 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 2 | 22 |
| 82D00706 | 12 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 1 | 17 |
| 82D00723 | 16 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 3 | 38 |
| 82D00728 | 12 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 1 | 17 |
| 82D00734 | 12 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 |
| 82D00739 | 16 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 |
| 82D00750 | 16 | 0 | 0 | 1 | 6 | 8 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 4 | 50 |
| 82D00752 | 16 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 3 | 38 |
| 83D00010 | 15 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 2 | 29 | 8 | 0 | 0 | 3 | 38 |
| 83D00016 | 14 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 |
| 83D00020 | 18 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 3 | 33 |
| 83D00024 | 17 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 1 | 11 |
| 83D00042 | 16 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 |
| 83D00044 | 14 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 1 | 14 | 7 | 0 | 0 | 0 | 0 |
| 83D00047 | 14 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 2 | 29 | 7 | 0 | 0 | 1 | 14 |
| 83D00050 | 12 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 2 | 33 | 6 | 0 | 0 | 1 | 17 |
| 83D00059 | 17 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 1 | 13 | 9 | 0 | 0 | 0 | 0 |
| 83D00073 | 18 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 1 | 11 |
| 83D00101 | 9 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 1 | 25 | 5 | 0 | 0 | 2 | 40 |

Incidence of External, Visceral, and Skeletal Examination Findings - 1.25 mg/kg/day MPP Animals

| Maternal ID | External | | | | | Visceral | | | | | Skeletal | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number Examined | Anomalies No. | % | Variants No. | % | Number Examined | Anomalies No. | % | Variants No. | % | Number Examined | Anomalies No. | % | Variants No. | % |
| 82D00689 | 9 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 2 | 40 |
| 82D00697 | 17 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 3 | 33 |
| 82D00700 | 15 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 |
| 82D00710 | 13 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 5 | 83 | 7 | 0 | 0 | 2 | 29 |
| 82D00715 | 16 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 1 | 13 |
| 82D00731 | 16 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 1 | 13 | 8 | 0 | 0 | 0 | 0 |
| 82D00735 | 4 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 50 |
| 82D00740 | 7 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 0 |
| 82D00745 | 13 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 4 | 57 |
| 82D00763 | 12 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 1 | 17 | 6 | 0 | 0 | 1 | 17 |
| 83D00003 | 14 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 |
| 83D00014 | 5 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 1 | 33 |
| 83D00031 | 5 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 50 | 3 | 0 | 0 | 2 | 66 |
| 83D00032 | 16 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 4 | 50 |
| 83D00037 | 19 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 0 | 10 | 0 | 0 | 0 | 0 |
| 83D00056 | 10 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 1 | 20 | 5 | 0 | 0 | 0 | 0 |
| 83D00060 | 15 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 |
| 83D00067 | 16 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 0 |
| 83D00077 | 16 | 1 | 6 | 0 | 0 | 8 | 1 | 13 | 2 | 25 | 8 | 0 | 0 | 3 | 38 |

Incidence of External, Visceral, and Skeletal Examination Findings - 0.12 mg/kg/day MPP Animals

| Maternal ID | External | | | | | Visceral | | | | | Skeletal | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number Examined | Anomalies No. | % | Variants No. | % | Number Examined | Anomalies No. | % | Variants No. | % | Number Examined | Anomalies No. | % | Variants No. | % |
| 82D00693 | 14 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 1 | 14 | 7 | 0 | 0 | 3 | 43 |
| 82D00714 | 15 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 |
| 82D00727 | 17 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 0 | 0 |
| 82D00729 | 12 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 1 | 17 | 6 | 0 | 0 | 0 | 0 |
| 82D00746 | 11 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 2 | 40 | 6 | 0 | 0 | 1 | 17 |
| 82D00764 | 6 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| 83D00004 | 13 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 1 | 17 | 7 | 0 | 0 | 3 | 43 |
| 83D00011 | 13 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 1 | 17 | 7 | 0 | 0 | 2 | 29 |
| 83D00015 | 15 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 2 | 29 | 8 | 0 | 0 | 2 | 25 |
| 83D00023 | 12 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 1 | 17 | 6 | 0 | 0 | 0 | 0 |
| 83D00025 | 15 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 |
| 83D00030 | 17 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 5 | 63 | 9 | 0 | 0 | 0 | 0 |
| 83D00034 | 17 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 9 | 0 | 0 | 2 | 22 |
| 83D00038 | 13 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 2 | 29 |
| 83D00043 | 11 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 1 | 17 |
| 83D00054 | 11 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 2 | 40 | 5* | 0 | 0 | 0 | 0 |
| 83D00069 | 16 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 4 | 50 |
| 83D00075 | 10 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 |
| 83D00078 | 17 | 0 | 0 | 0 | 0 | 8 | 0 | 0 | 2 | 25 | 9 | 0 | 0 | 0 | 0 |
| 83D00080 | 14 | 0 | 0 | 0 | 0 | 7 | 0 | 0 | 1 | 14 | 7 | 0 | 0 | 0 | 0 |
| 83D00097 | 11 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 |

*One fetus lost during skeletal staining process.

Incidence of Anomalies and Variants
Vehicle Animals

| Maternal ID | Number Examined | Anomalies No. | Anomalies % | Variants No. | Variants % |
|---|---|---|---|---|---|
| 82D00682 | 9 | 0 | 0 | 0 | 0 |
| 82D00691 | 17 | 0 | 0 | 4 | 24 |
| 82D00698 | 14 | 0 | 0 | 0 | 0 |
| 82D00703 | 1 | 1 | 100 | 1 | 100 |
| 82D00719 | 15 | 0 | 0 | 0 | 0 |
| 82D00724 | 6 | 0 | 0 | 0 | 0 |
| 82D00743 | 12 | 0 | 0 | 7 | 58 |
| 82D00751 | 9 | 0 | 0 | 2 | 22 |
| 83D00001 | 9 | 0 | 0 | 2 | 22 |
| 83D00019 | 18 | 0 | 0 | 6 | 33 |
| 83D00039 | 7 | 0 | 0 | 0 | 0 |
| 83D00062 | 19 | 0 | 0 | 8 | 42 |
| 83D00063 | 14 | 0 | 0 | 1 | 7 |
| 83D00070 | 18 | 0 | 0 | 2 | 11 |
| 83D00076 | 17 | 0 | 0 | 0 | 0 |
| 83D00082 | 14 | 0 | 0 | 5 | 36 |
| 83D00096 | 16 | 0 | 0 | 5 | 31 |

Incidence of Anomalies and Variants
3.12 mg/kg/day MPP Animals

| Maternal ID | Number Examined | Anomalies No. | Anomalies % | Variants No. | Variants % |
|---|---|---|---|---|---|
| 82D00681 | 14 | 0 | 0 | 2 | 14 |
| 82D00696 | 13 | 0 | 0 | 1 | 8 |
| 82D00699 | 7 | 0 | 0 | 0 | 0 |
| 82D00704 | 17 | 0 | 0 | 2 | 12 |
| 82D00706 | 12 | 0 | 0 | 1 | 8 |
| 82D00723 | 16 | 0 | 0 | 3 | 19 |
| 82D00728 | 12 | 0 | 0 | 1 | 8 |
| 82D00734 | 12 | 0 | 0 | 0 | 0 |
| 82D00739 | 16 | 0 | 0 | 0 | 0 |
| 82D00750 | 16 | 0 | 0 | 5 | 31 |
| 82D00752 | 16 | 0 | 0 | 3 | 19 |
| 83D00010 | 15 | 0 | 0 | 5 | 33 |
| 83D00016 | 14 | 0 | 0 | 0 | 0 |
| 83D00020 | 18 | 0 | 0 | 3 | 17 |
| 83D00024 | 17 | 0 | 0 | 1 | 6 |
| 83D00042 | 16 | 0 | 0 | 0 | 0 |
| 83D00044 | 14 | 0 | 0 | 1 | 7 |
| 83D00047 | 14 | 0 | 0 | 3 | 21 |
| 83D00050 | 12 | 0 | 0 | 3 | 25 |
| 83D00059 | 17 | 0 | 0 | 1 | 6 |
| 83D00073 | 18 | 0 | 0 | 1 | 6 |
| 83D00101 | 9 | 0 | 0 | 3 | 33 |

Incidence of Anomalies and Variants
1.25 mg/kg/day MPP Animals

| Maternal ID | Number Examined | Anomalies No. | Anomalies % | Variants No. | Variants % |
|---|---|---|---|---|---|
| 82D00689 | 9 | 0 | 0 | 2 | 22 |
| 82D00697 | 17 | 0 | 0 | 3 | 18 |
| 82D00700 | 15 | 0 | 0 | 0 | 0 |
| 82D00710 | 13 | 0 | 0 | 7 | 54 |
| 82D00715 | 16 | 0 | 0 | 1 | 6 |
| 82D00731 | 16 | 0 | 0 | 1 | 6 |
| 82D00735 | 4 | 0 | 0 | 1 | 25 |
| 82D00740 | 7 | 0 | 0 | 0 | 0 |
| 82D00745 | 13 | 0 | 0 | 4 | 31 |
| 82D00763 | 12 | 0 | 0 | 2 | 17 |
| 83D00003 | 14 | 0 | 0 | 0 | 0 |
| 83D00014 | 5 | 0 | 0 | 1 | 20 |
| 83D00031 | 5 | 0 | 0 | 3 | 60 |
| 83D00032 | 16 | 0 | 0 | 4 | 25 |
| 83D00037 | 19 | 0 | 0 | 0 | 0 |
| 83D00056 | 10 | 0 | 0 | 1 | 10 |
| 83D00060 | 15 | 0 | 0 | 0 | 0 |
| 83D00067 | 16 | 0 | 0 | 0 | 0 |
| 83D00077 | 16 | 1 | 6 | 5 | 31 |

Incidence of Anomalies and Variants
0.12 mg/kg/day MPP Animals

| Maternal ID | Number Examined | Anomalies No. | Anomalies % | Variants No. | Variants % |
|---|---|---|---|---|---|
| 82D00693 | 14 | 0 | 0 | 4 | 29 |
| 82D00714 | 15 | 0 | 0 | 0 | 0 |
| 82D00727 | 17 | 0 | 0 | 0 | 0 |
| 82D00729 | 12 | 0 | 0 | 1 | 8 |
| 82D00746 | 11 | 0 | 0 | 3 | 27 |
| 82D00764 | 6 | 0 | 0 | 0 | 0 |
| 83D00004 | 13 | 0 | 0 | 4 | 31 |
| 83D00011 | 13 | 0 | 0 | 3 | 23 |
| 83D00015 | 15 | 0 | 0 | 4 | 27 |
| 83D00023 | 12 | 0 | 0 | 1 | 8 |
| 83D00025 | 15 | 0 | 0 | 0 | 0 |
| 83D00030 | 17 | 0 | 0 | 5 | 29 |
| 83D00034 | 17 | 0 | 0 | 2 | 12 |
| 83D00038 | 13 | 0 | 0 | 2 | 15 |
| 83D00043 | 11 | 0 | 0 | 1 | 9 |
| 83D00054 | 11* | 0 | 0 | 2 | 18 |
| 83D00069 | 16 | 0 | 0 | 4 | 25 |
| 83D00075 | 10 | 0 | 0 | 0 | 0 |
| 83D00078 | 17 | 0 | 0 | 2 | 12 |
| 83D00080 | 14 | 0 | 0 | 1 | 7 |
| 83D00097 | 11 | 0 | 0 | 0 | 0 |

*One fetus lost during processing not included in skeletal examination.

## Fetal Ossification Data - Vehicle Animals

| Maternal ID | No. Fetuses | Mean Number Ossified | | | |
|---|---|---|---|---|---|
| | | Sternebrae | Caudal Vertebrae | Metacarpals | Metatarsals |
| 82D00682 | 5 | 6.00 | 5.25 | 8.00 | 8.00 |
| 82D00691 | 9 | 5.78 | 3.56 | 6.44 | 7.78 |
| 82D00698 | 7 | 5.57 | 2.86 | 6.00 | 7.43 |
| 82D00703 | 1 | 6.00 | 4.00 | 8.00 | 8.00 |
| 82D00719 | 8 | 6.00 | 5.00 | 8.00 | 8.25 |
| 82D00724 | 3 | 6.00 | 6.67 | 8.00 | 10.00 |
| 82D00743 | 6 | 6.00 | 3.17 | 6.00 | 8.00 |
| 82D00751 | 4 | 4.75 | 3.25 | 6.00 | 8.00 |
| 83D00001 | 5 | 5.40 | 4.00 | 6.00 | 8.00 |
| 83D00019 | 9 | 5.22 | 3.00 | 6.44 | 8.00 |
| 83D00039 | 4 | 5.00 | 2.25 | 6.50 | 8.00 |
| 83D00062 | 9 | 4.89 | 2.33 | 6.00 | 8.00 |
| 83D00063 | 7 | 5.43 | 4.14 | 6.86 | 8.00 |
| 83D00070 | 9 | 4.89 | 3.00 | 6.00 | 8.00 |
| 83D00076 | 9 | 5.11 | 3.00 | 6.00 | 8.00 |
| 83D00082 | 7 | 5.14 | 3.43 | 6.00 | 7.86 |
| 83D00096 | 8 | 4.63 | 3.25 | 6.00 | 8.00 |

Fetal Ossification Data - 3.13 mg/kg/day MPP Animals

| Maternal ID | No. Fetuses | Mean Number Ossified | | | |
|---|---|---|---|---|---|
| | | Sternebrae | Caudal Vertebrae | Metacarpals | Metatarsals |
| 82D00681 | 7 | 6.00 | 6.14 | 8.00 | 10.00 |
| 82D00696 | 7 | 5.57 | 3.14 | 6.57 | 8.00 |
| 82D00699 | 4 | 5.75 | 3.25 | 6.50 | 8.00 |
| 82D00704 | 9 | 6.00 | 3.33 | 6.89 | 8.00 |
| 82D00706 | 6 | 5.67 | 3.00 | 6.00 | 8.00 |
| 82D00723 | 8 | 5.88 | 3.38 | 7.00 | 8.00 |
| 82D00728 | 5 | 5.20 | 3.00 | 6.00 | 8.00 |
| 82D00734 | 6 | 6.00 | 6.67 | 8.00 | 9.67 |
| 82D00739 | 8 | 5.88 | 4.25 | 7.75 | 8.00 |
| 82D00750 | 8 | 5.50 | 3.38 | 6.25 | 8.00 |
| 82D00752 | 8 | 5.88 | 3.50 | 7.00 | 8.00 |
| 83D00010 | 8 | 5.00 | 3.13 | 6.00 | 8.00 |
| 83D00016 | 7 | 5.57 | 3.86 | 6.00 | 8.00 |
| 83D00020 | 9 | 4.89 | 4.00 | 6.00 | 8.00 |
| 83D00024 | 9 | 4.67 | 3.44 | 5.78 | 7.11 |
| 83D00042 | 8 | 5.00 | 3.00 | 6.00 | 7.50 |
| 83D00044 | 7 | 5.57 | 3.14 | 6.00 | 8.00 |
| 83D00047 | 7 | 5.14 | 3.00 | 6.00 | 8.00 |
| 83D00050 | 6 | 6.00 | 3.00 | 6.67 | 8.00 |
| 83D00059 | 9 | 5.78 | 3.56 | 6.00 | 8.00 |
| 83D00073 | 9 | 4.11 | 2.44 | 5.78 | 7.78 |
| 83D00101 | 5 | 4.80 | 1.80 | 6.00 | 8.00 |

Fetal Ossification Data - 1.25 mg/kg/day MPP Animals

| Maternal ID | No. Fetuses | Mean Number Ossified | | | |
|---|---|---|---|---|---|
| | | Sternebrae | Caudal Vertebrae | Metacarpals | Metatarsals |
| 82D00689 | 5 | 5.80 | 3.80 | 6.00 | 8.00 |
| 82D00697 | 9 | 5.78 | 4.00 | 6.00 | 8.00 |
| 82D00700 | 8 | 6.00 | 4.88 | 8.00 | 9.75 |
| 82D00710 | 7 | 6.00 | 3.29 | 6.29 | 8.00 |
| 82D00715 | 8 | 6.00 | 3.13 | 6.00 | 8.00 |
| 82D00731 | 8 | 5.75 | 3.25 | 6.00 | 8.00 |
| 82D00735 | 2 | 6.00 | 3.50 | 8.00 | 8.00 |
| 82D00740 | 4 | 5.25 | 2.25 | 6.00 | 7.50 |
| 82D00745 | 7 | 6.00 | 6.29 | 8.00 | 10.00 |
| 82D00763 | 6 | 5.00 | 2.67 | 6.00 | 7.33 |
| 83D00003 | 7 | 4.86 | 3.29 | 6.00 | 8.00 |
| 83D00014 | 3 | 5.67 | 4.33 | 6.00 | 8.00 |
| 83D00031 | 3 | 5.33 | 3.00 | 7.33 | 8.00 |
| 83D00032 | 8 | 5.13 | 3.13 | 6.00 | 8.00 |
| 83D00037 | 10 | 5.60 | 3.40 | 6.00 | 8.00 |
| 83D00056 | 5 | 5.20 | 3.00 | 6.40 | 8.00 |
| 83D00060 | 8 | 5.13 | 3.25 | 6.00 | 8.00 |
| 83D00067 | 9 | 4.11 | 3.22 | 6.00 | 7.56 |
| 83D00077 | 8 | 5.00 | 3.00 | 6.25 | 8.00 |

Fetal Ossification Data 0.12 mg/kg/day MPP Animals

| Maternal ID | No. Fetuses | Mean Number Ossified | | | |
|---|---|---|---|---|---|
| | | Sternebrae | Caudal Vertebrae | Metacarpals | Metatarsals |
| 82D00693 | 7 | 6.00 | 3.00 | 6.00 | 8.00 |
| 82D00714 | 7 | 6.00 | 6.14 | 8.00 | 10.00 |
| 82D00727 | 9 | 6.00 | 3.67 | 8.00 | 8.00 |
| 82D00729 | 6 | 5.50 | 3.00 | 6.00 | 8.00 |
| 82D00746 | 6 | 6.00 | 4.33 | 8.00 | 8.00 |
| 82D00764 | 3 | 6.00* | 3.00 | 6.00 | 8.00 |
| 83D00004 | 7 | 5.00 | 6.00 | 6.00 | 8.00 |
| 83D00011 | 7 | 5.14 | 3.43 | 6.00 | 8.00 |
| 83D00015 | 8 | 4.38 | 3.00 | 6.25 | 8.00 |
| 83D00023 | 6 | 4.83 | 3.17 | 6.00 | 8.00 |
| 83D00025 | 8 | 5.38 | 3.88 | 6.50 | 8.00 |
| 83D00030 | 9 | 4.22 | 2.22 | 6.00 | 7.78 |
| 83D00034 | 9 | 4.22 | 2.44 | 5.56 | 7.78 |
| 83D00038 | 7 | 5.71 | 6.71 | 8.00 | 10.00 |
| 83D00043 | 6 | 5.67 | 2.17 | 6.67 | 8.00 |
| 83D00054 | 5 | 6.00 | 5.60 | 8.00 | 8.00 |
| 83D00069 | 8 | 4.00 | 3.13 | 5.63 | 8.00 |
| 83D00075 | 5 | 5.80 | 3.60 | 6.00 | 8.00 |
| 83D00078 | 9 | 4.11 | 2.00 | 6.00 | 8.00 |
| 83D00080 | 8 | 3.75 | 3.00 | 6.00 | 8.00 |
| 83D00097 | 6 | 5.33 | 4.17 | 7.33 | 8.00 |

*Sternebrae of 1 fetus damaged in processing not included in sternebrae litter mean.

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